Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

3rd degree of biomimetism: associating cavity effect, Zn^{II} coordination *and* internal base assistance for guest binding and activation

Arnaud Parrot, Solène Collin, Gilles Bruylants, and Olivia Reinaud

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, CNRS UMR 8601, Université Paris Descartes, PRES Sorbonne Paris Cité, 45 rue des Saints Pères, 75006 Paris, France.

1. Synthesis and Characterization of Rim_4 and Corresponding Zn^{II} Complexes

General: solvents and reagents were obtained commercially. DMF (anhydrous 99.8 %) was stored over 4 Å molecular sieves and under Argon. THF was freshly distilled over sodium/benzophenone under Argon. Resorcinarene tetra(alcohol) **1** and 2-chloromethyl-1-methyl-1*H*-imidazole were synthesized according to literature procedures.[1,2] NMR spectra were recorded with a Varian VNMRS 600 MHz spectrometer, Bruker ARX 250 MHz spectrometer or an Advance 500 spectrometer (500 MHz). Standard HSQC and HMBC experiments were used for peak assignments. MS (ESI) analyses were obtained with a ThermoFinnigen LCQ Advantage spectrometer using methanol, dichloromethane or acetonitrile as solvents. IR spectra were obtained with a Perkin-Elmer Spectrum on FTIR spectrometer equipped with a MIRacleTM single reflection horizontal ATR unit (germanium crystal).

Safety note. Caution! Although we have not encountered any problems, it is noted that perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled only in small quantities and with appropriate precautions.

Tetra(imidazole) cavitand Rim_4

Tetra(alcohol)cavitand **1** (0.45 mmol; 420 mg) was dissolved in freshly distilled THF (4 mL). The solution was evaporated under vacuum at 80 °C for 1 h in order to eliminate traces of water. This operation was repeated 3 times. Under argon at 0 °C, compound **1** was then dissolved in dry DMF (8 mL) and added dropwise to a suspension of NaH (14 mmol; 544 mg of a 60% dispersion washed with n-pentane) in dry DMF (5 mL). The reaction mixture was then stirred for 30 min at 0 °C and two additional hours at room temperature. At 0 °C, 2-chloromethyl-1-methyl-1*H*-imidazole (3.6 mmol; 606 mg) was added in 4 portions into the mixture every 15 min. The resulting orange suspension was stirred overnight at room temperature. The mixture was hydrolyzed at 0 °C with water (60 mL). The resulting solid was filtered off, washed with water (2 x 20 mL), then ammonia 2% (20 mL) and water (20 mL). The resulting powder was redissolved in dichloromethane (10 mL), dried over Na_2SO_4, filtered and evaporated to yield an off-white solid (511 mg). This solid was purified over silica (DCM/MeOH 9:1 to 8:2 with 0.3 % NH_3). The solid obtained was dissolved in 3 mL chloroform and washed with NaOH 1 M (2 mL) and twice with water (2 mL). The organic layer was dried over Na_2SO_4 and evaporated. The obtained solid was recristallized from EtOH/H_2O 1:1 (4 mL) to yield an off-white powder (389 mg, 64%).

R_f = 0.44 (CH_2Cl_2/MeOH 9:1, 0.3% NH_3).

^{1}H NMR (600 MHz, $CDCl_3$, 300 K, TMS): δ =7.03 (s, 4H; $H_{Ar,down}$), 6.93 (s, 4H; $H_{Im,\alpha}$), 6.89 (s, 4H; $H_{Im,\beta}$), 5.57 (d, ^2J(H, H) =7.2 Hz, 4H; H_{bridge}), 4.70 (t, ^3J(H, H) = 8.4 Hz, 4H; C*H*-CH_2), 4.56 (s, 8H; CH_2-Im), 4.20 (s, 8H; Ar-CH_2-O), 4.16 (d, ^2J(H, H) =7.2 Hz, 4H; H_{bridge}), 3.62 (s, 12H; NCH_3), 2.13 (m, 8H; CH-CH_2-CH_2), 1.34 (m, 24H; (CH_2)$_3$-CH_3), 0.88 ppm (t, ^3J(H, H) =7.2 Hz, 12H; CH_3).

^{13}C NMR (150 MHz, CD_3CN, 300 K, TMS): δ =154.8 (*C*-O ring), 145.6 (N-*C*=N imidazole), 139.4 (*C*-CH ring), 127.9 (*C*H-N imidazole), 125.7 (*C*H ring down), 123.3 (*C*H-NMe imidazole), 122.8 (*C*-CH_2 ring), 100.7 (O-*C*H_2-O), 65.1 (*C*H_2-C Imidazole), 62.2 (*C*H_2-O), 38.3 (*C*H), 33.2 (*C*H_2-CH_3), 32.8 (*C*H_3-N), 30.5 (*C*H_2-CH_2-CH), 28.4 (*C*H_2-CH), 23.3 (CH_2-*C*H_2-CH_3), 14.5 ppm (*C*H_3).

IR: ν = 2925.8, 2856.2, 1654.5, 1590.1, 1499.1, 1458.5, 1400.1, 1347.6, 1284.3, 1241.5, 1149.4, 1066.7, 968.5, 746.9 cm^{-1}.

HR MS (ESI): *m/z*: [**Rim_4** + H]$^+$ calcd. $C_{76}H_{97}N_8O_{12}$ 1313.7226, found 1313.7207; [**Rim_4** + 2H]$^{2+}$ calcd. $C_{76}H_{98}N_8O_{12}$ 657.3652, found 657.3635.

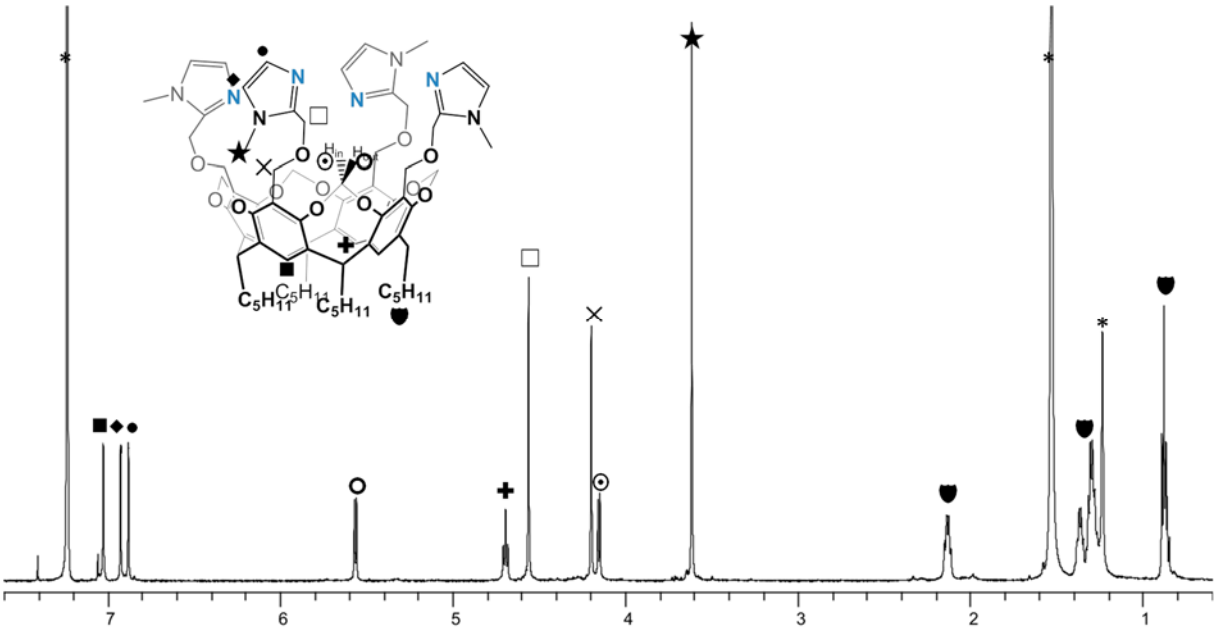

Figure S1. ^{1}H NMR spectrum of **Rim$_4$** (600 MHz, $CDCl_3$, 300 K, TMS).* solvent and grease.

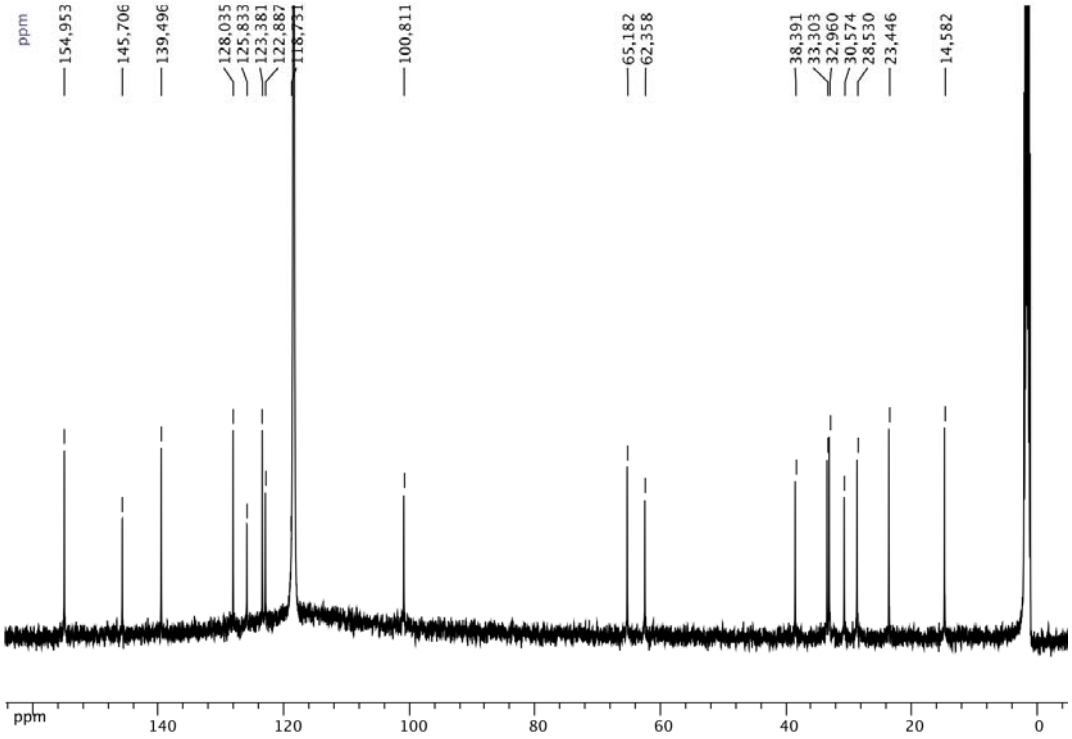

Figure S2. ^{13}C NMR spectrum (150 MHz, CD_3CN, 300 K) of **Rim$_4$**.

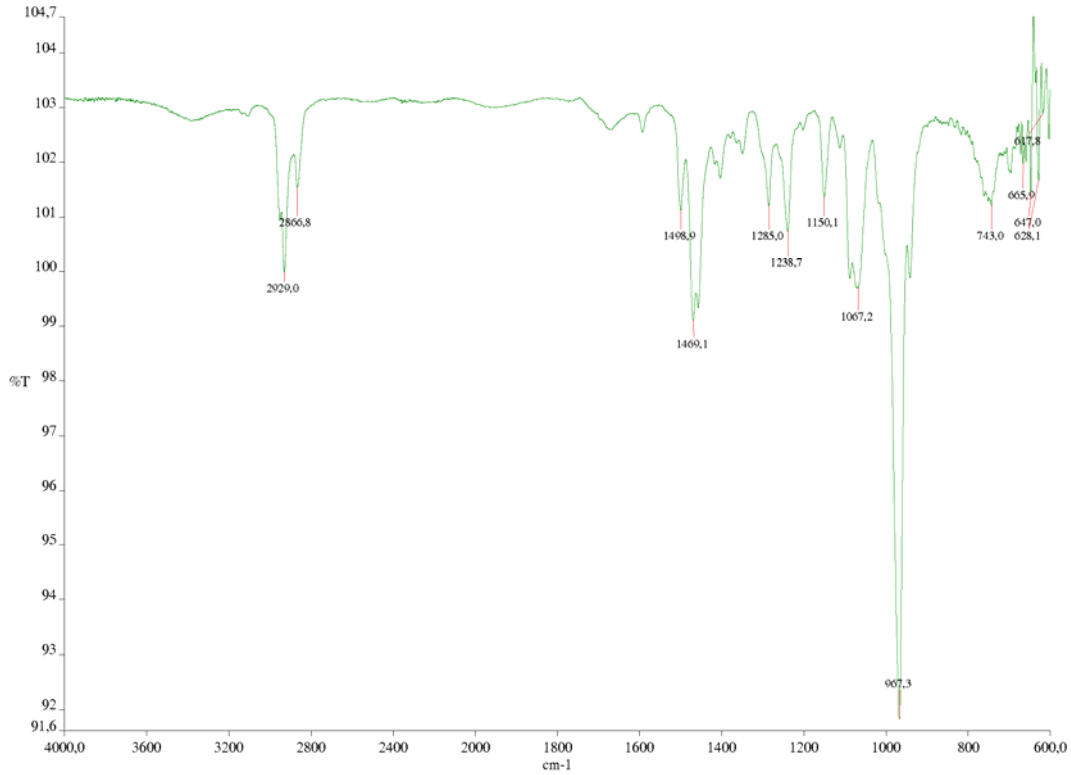

Figure S3. IR spectrum of **Rim$_4$**.

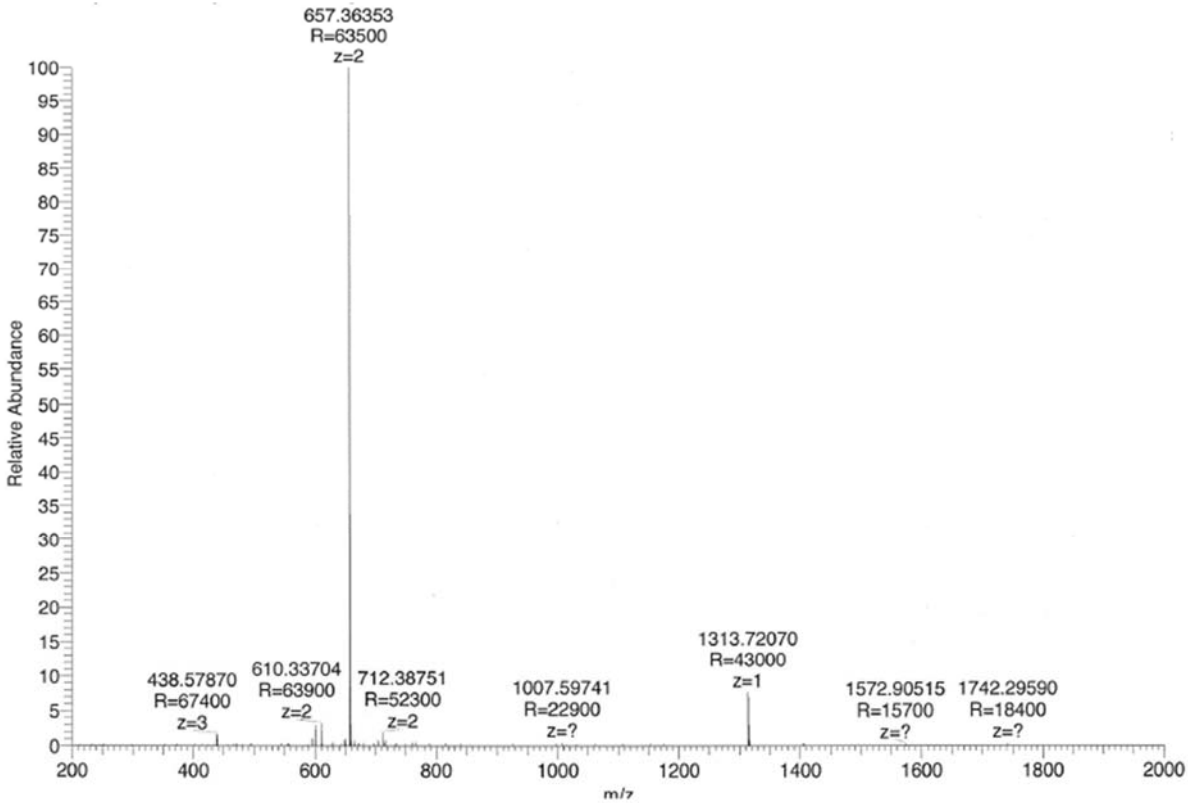

Figure S4. High-resolution ESI+ mass spectra of **Rim$_4$** in acetonitrile.

Zinc complex [Rim$_4$Zn(EtOH)](ClO$_4$)$_2$

Ligand **Rim$_4$** (0.035 mmol; 46 mg) was dissolved in degassed EtOH (1 mL) under argon and added dropwise to a solution of $Zn(ClO_4)_2.6H_2O$ (0.035 mmol; 13 mg) in degassed EtOH (1 mL). A white solid precipitated during the addition and the resulting mixture was stirred for an additional hour under argon. After centrifugation, the white solid was separated, washed twice with EtOH (1mL) and then dried under vacuum at 60 °C for 2 h, yielding a white solid (48 mg, 85%).

The NMR of the solid revealed the presence of 1 eq EtOH that is likely bound to the Zn^{II} center when the complex precipitates and replaced by acetonitrile when dissolved in this solvent.

^{1}H NMR (500 MHz, CD_3CN, 300 K, TMS): δ =7.39 (s, 4H; $H_{Ar,down}$), 7.11 (s, 4H; $H_{Im,\alpha}$), 6.48 (s, 4H; $H_{Im,\beta}$), 5.71 (d, ^2J(H, H) =7.2 Hz, 4H; H_{bridge}), 4.74 (t, ^3J(H, H) = 8.2 Hz, 4H; C*H*-CH_2), 4.58 (s, 8H; CH_2-Im), 4.19 (d, ^2J(H, H) =7.2 Hz, 4H; H_{bridge}), 4.11 (s, 8H; Ar-CH_2-O), 3.78 (s, 12H; NCH_3), 2.33 (m, 8H; CH-C*H*$_2$-CH_2), 1.39 (m, 24H; (C*H*$_2$)$_3$-CH_3), 0.92 ppm (t, ^3J(H, H) = 6.9 Hz, 12H; CH_3).

^{13}C NMR (150 MHz, CD_3CN, 300 K, TMS): δ = 154.7 (*C*-O Ring); 146.7 (N-*C*=N Imidazole); 139.8 (*C*-CH Ring); 126.7 (*C*H-N Imidazole); 124.7 (*C*H-NMe Imidazole); 123.3 (*C*H ring); 100.8 (O-*C*H_2-O); 65.0 (*C*H_2-Imidazole); 63.0 (*C*H_2-O); 38.4 (*C*H); 34.9 (*C*H_3-N); 32.9 (*C*$H_2CH_2CH_3$); 30.2 (*C*$H_2(CH_2)_3CH_3$); 28.4 (*C*$H_2(CH_2)_2CH_3$); 23.4 (*C*H_2CH_3); 14.6 ppm (*C*H_3).

IR: ν = 2929.2, 2861.0, 1634.5, 1591.8, 1506.0, 1457.0, 1287.8, 1242.5, 1151.5, 1087.3, 1019.6, 970.3, 755.0, 667.7, 623.6 (ClO_4^-), 587.0 cm^{-1}.

HR-MS (ESI): *m/z*: [**Rim$_4$**ZnCl]$^+$ calcd. 1411.6128, found 1411.6113; [**Rim$_4$**Zn(HCOO)]$^+$ calcd. 1421.6416, found 1421.6372; [**Rim$_4$**Zn(OAc)]$^+$ calcd. 1435.6572, found 1435.6541. *Note:* the anions bound to the detected Zn^{II} complex come from the electrospray apparatus.

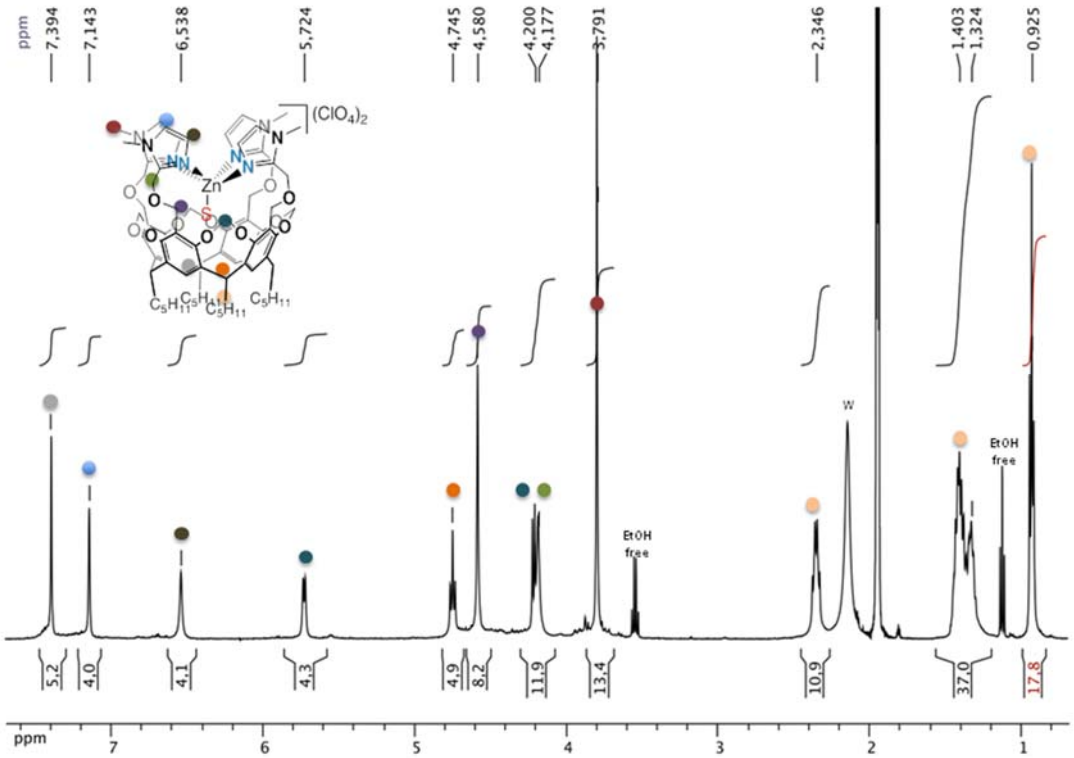

Figure S5. ^{1}H NMR spectrum (CD_3CN, 300 K, 500 MHz) of [**Rim$_4$**Zn(S)]$(ClO_4)_2$, as isolated (S = EtOH in the solid, S = MeCN in MeCN).

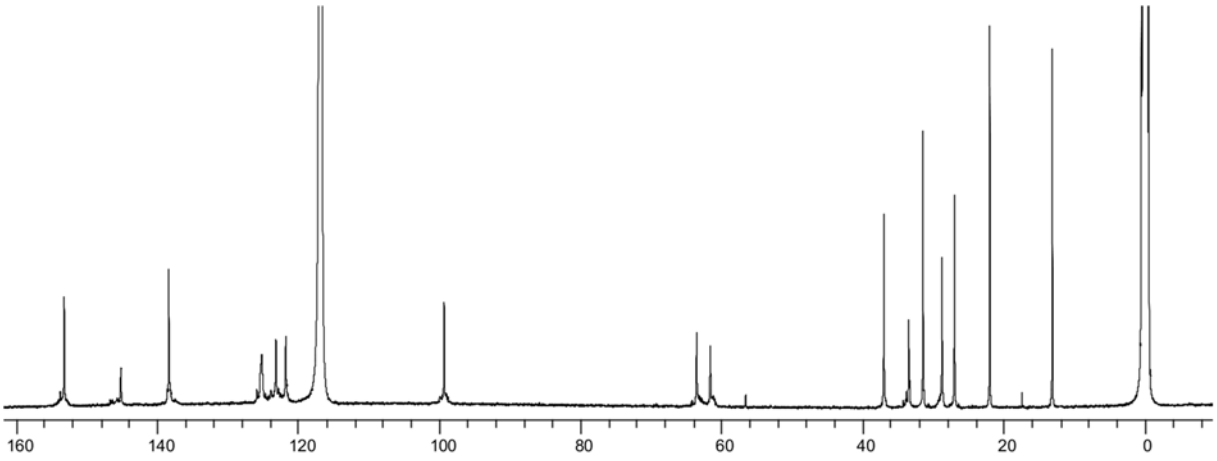

Figure S6. ^{13}C NMR spectrum (150 MHz, CD_3CN, 300 K) of [**Rim**$_4$Zn(S)]$(ClO_4)_2$.

Figure S7. IR spectrum of [**Rim**$_4$Zn(EtOH)]$(ClO_4)_2$.

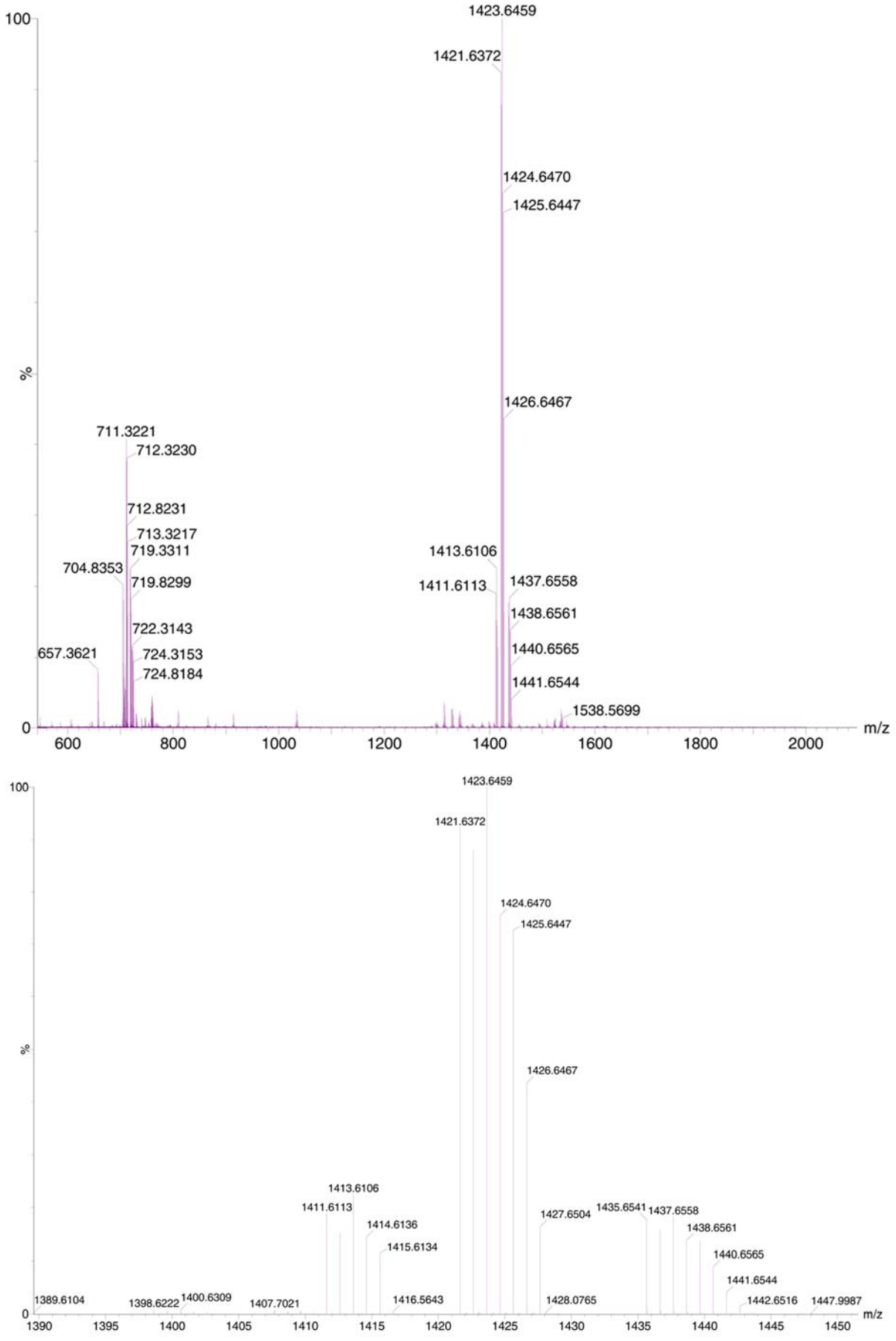

Figure S8. HR-MS ESI+ spectra of [**Rim**$_4$Zn(S)](ClO$_4$)$_2$ in acetonitrile.

Acetato Zinc complex [Rim$_4$Zn(OAc)](ClO$_4$)

[**Rim$_4$**Zn(EtOH)](ClO$_4$)$_2$ (0.0057 mmol; 9 mg) was dissolved in acetonitrile (2 mL) and NaOAc (excess, ca. 1 mg as a solid) was added to the solution. The resulting suspension was sonicated then stirred for 20 minutes. The suspension was filtered via a syringe filter, evaporated, washed with water (2 mL), then dried under vacuum yielding a tanned powder (8.7 mg, 99%).

^{1}H NMR (500 MHz, CD_3CN, 300 K, TMS): δ = 7.43 (s, 4H; $H_{Ar,down}$), 7.08 (s, 4H; $H_{Im,\alpha}$), 6.68 (s, 4H; $H_{Im,\beta}$), 5.62 (d, ^2J(H, H) = 7.3 Hz, 4H; H_{bridge}), 4.72 (t, ^3J(H, H) = 8.2 Hz, 4H; C*H*-CH_2), 4.45 (s, 8H; CH_2-Im), 4.40 (d, ^2J(H, H) = 7.3 Hz, 4H; H_{bridge}), 4.32 (s, 8H; Ar-CH_2-O), 3.69 (s, 12H; NCH_3), 2.37 (m, 8H; CH-C*H*$_2$-CH_2), 1.40-1.37 (m, 24H; (C*H*$_2$)$_3$-CH_3), 0.93 (t, ^3J(H, H) = 7.0 Hz, 12H; CH_3), –2.40 ppm (s, 3H; *endo*-bound CH_3COO^-).

^{13}C NMR (150 MHz, CD_3CN, 300 K, TMS): δ = 155.6 (C-O Ring), 146.8 (N-C=N), 138.6 (C-CH Ring), 126.2 (CH-N), 125.3 (CH-NMe), 124.5 (CH_{Ar}), 123.8 (C-CH_2O), 101.6 (O-CH_2-O), 64.3 (C-CH_2-O), 63.8 (CH_2-Imidazole), 38.5 (CH), 34.3 (N-CH_3), 32.9 (CH_2-CH_2-CH_3), 30.7 (CH-CH_2-$(CH_2)_3$-CH_3), 28.6 (CH_2-$(CH_2)_2$-CH_3), 23.4 (CH_2-CH_3), 14.5 ppm (CH_3); IR: ν=2935.8, 2865.3, 1590.3, 1458.7, 1290.1, 1241.2, 1150.6, 1087.8, 1018.6, 965.9, 882.3, 756.8, 680.8, 623.6 (ClO_4^-), 586.5 cm^{-1}. HR-MS (ESI): *m/z*: calcd. 1435.6572, found 1435.6555 [**Rim$_4$**Zn(OAc)]$^+$.

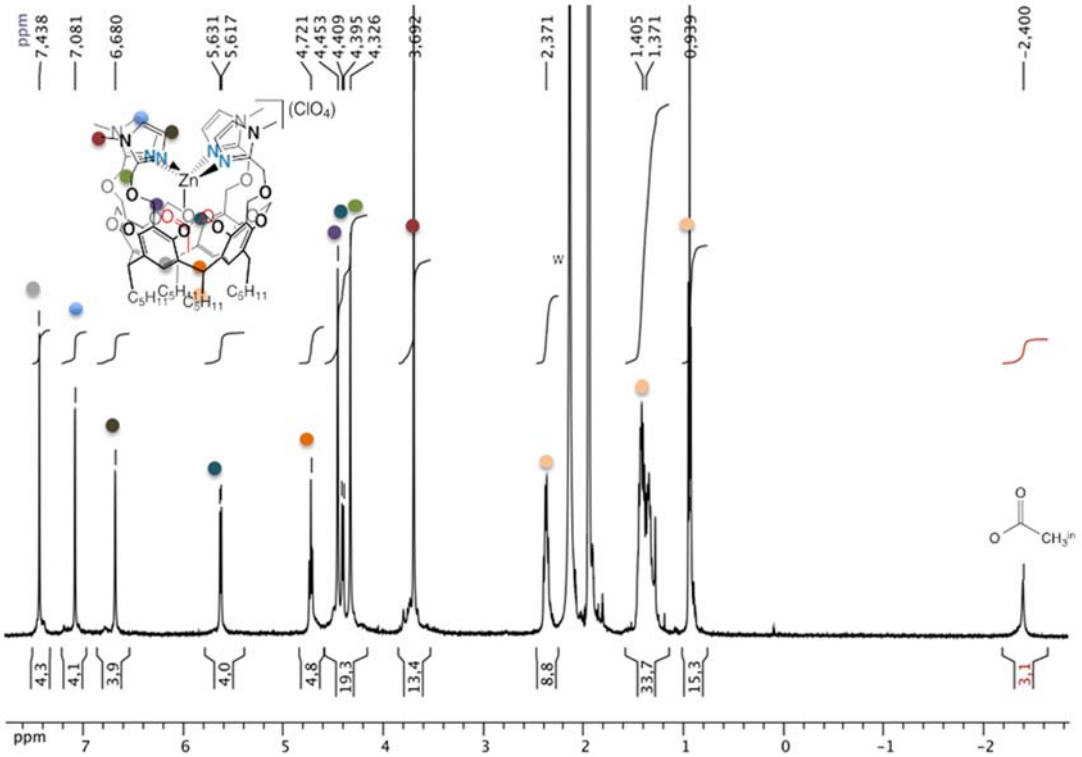

Figure S9. ^{1}H NMR spectrum (CD_3CN, 300 K, 500 MHz) of [**Rim$_4$**Zn(OAc)](ClO$_4$).

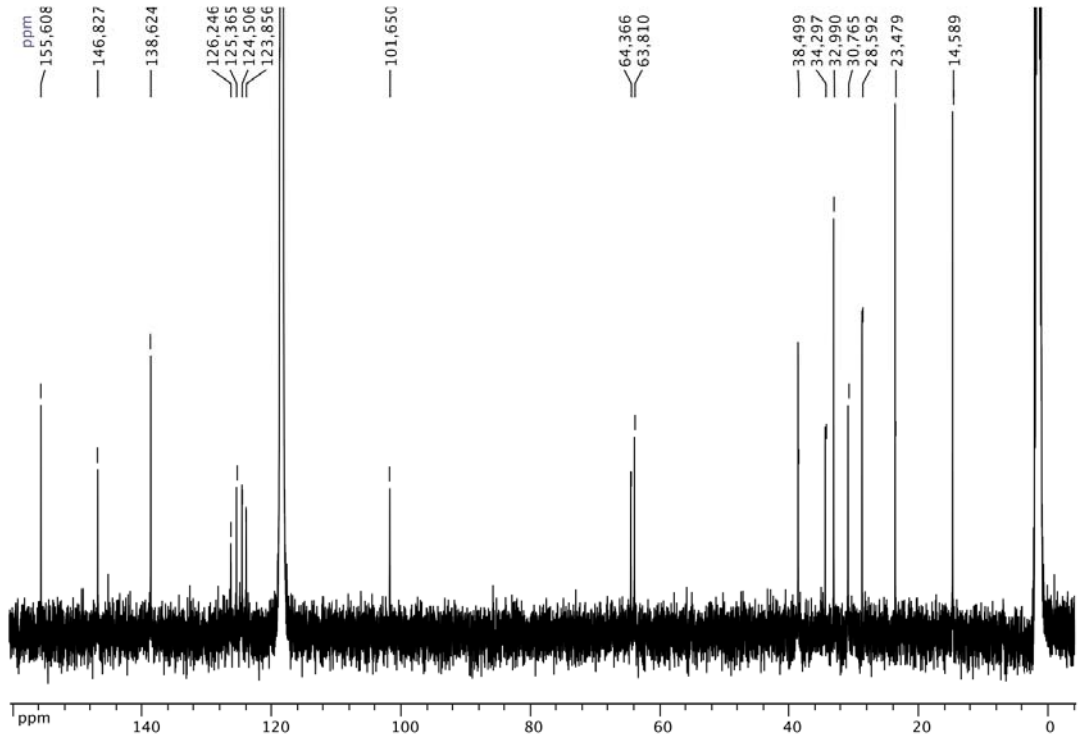

Figure S10. ^{13}C NMR spectrum (150 MHz, CD_3CN, 300 K) of [**Rim**$_4$Zn(OAc)](ClO_4).

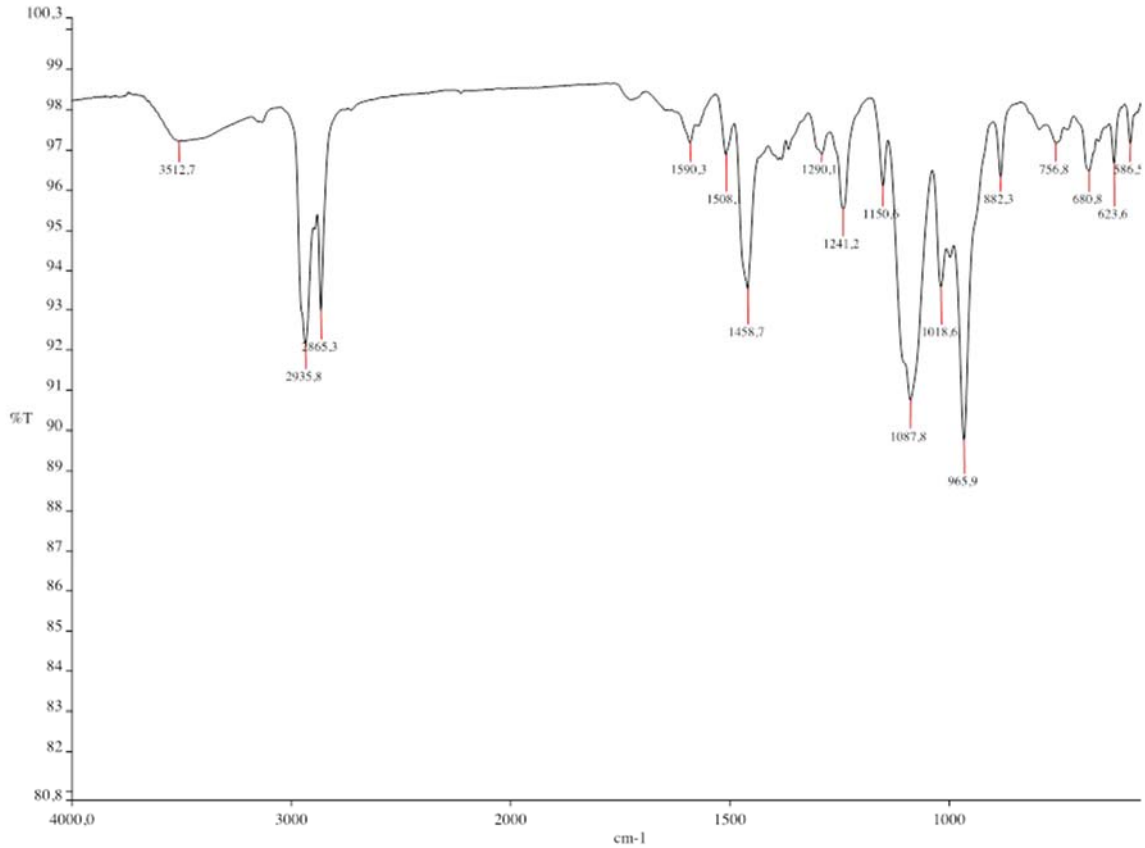

Figure S11. IR spectrum of [**Rim**$_4$Zn(OAc)](ClO_4), KBr pellet.

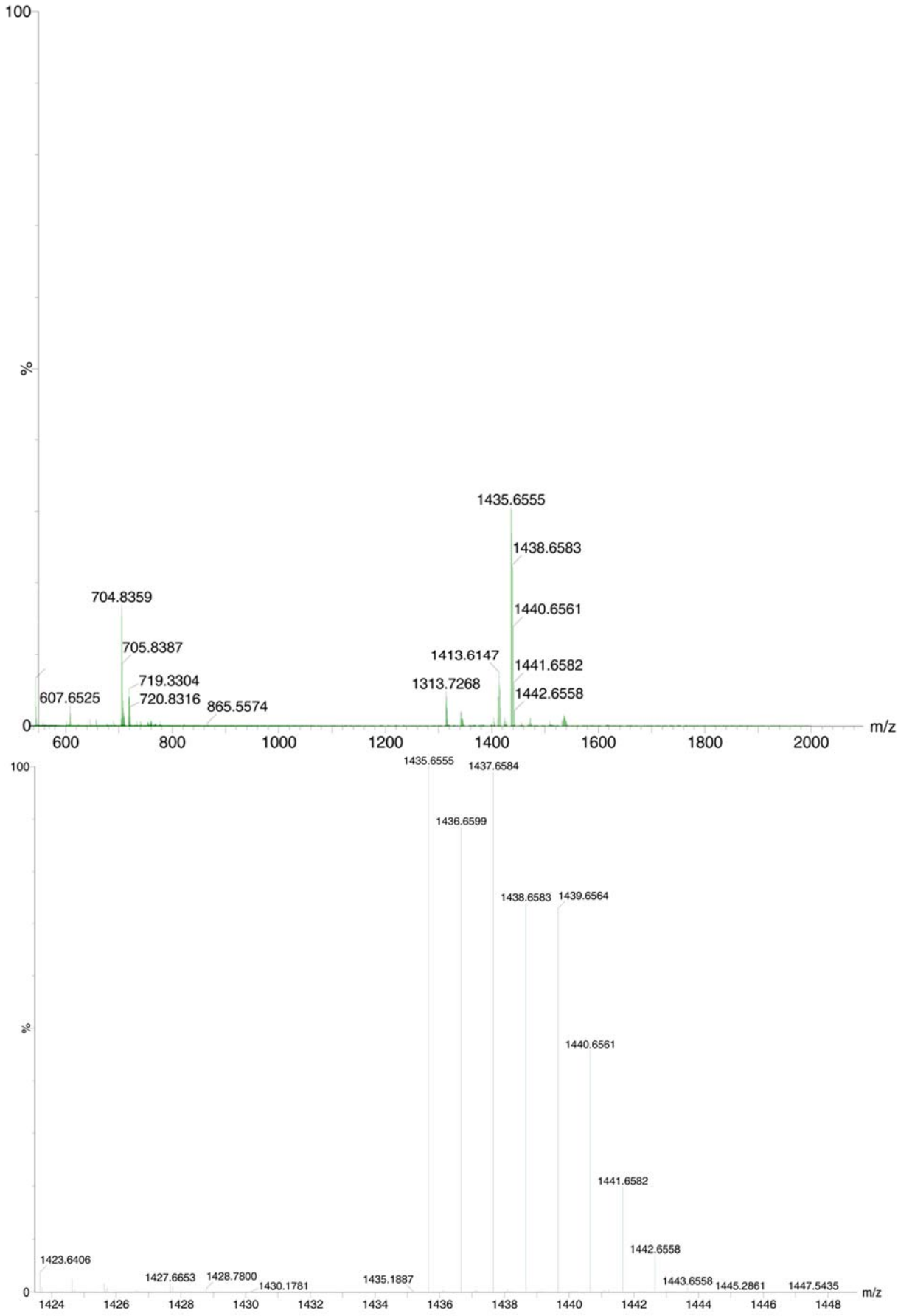

Figure S12. ESI+ Mass spectrum of [**Rim**$_4$Zn(OAc)](ClO$_4$) in acetonitrile.

Acetamido Zinc complex [Rim$_4$Zn(NHAc)](ClO$_4$)

The acetamido complex was generated in MeCN solution by addition of acetamide and Et_3N (1 eq of each or more) to a solution of the **Rim$_4$**Zn dicationic complex in MeCN.

Heating a MeCN solution of the **Rim$_4$**Zn dicationic complex at 70°C for 6 days produces the acetamido adduct with one protonated imidazole arm, [**Rim$_4$**HZn(NHAc)]$^{2+}$, which is quantitatively transformed into the monocationic complex [**Rim$_4$**Zn(NHAc)]$^+$ upon addition of 1 eq of Et_3N.

It was characterized by ^{1}H NMR (in acetonitrile, see the main text, Figure 6 and Figures S29-S35) by the peak at -2.40 ppm accounting for the presence of one equivalent relative to the resorcinarene core of acetamide bound in the cavity. The latter is readily displaced by acetate through addition of AcOH.

2. DOSY Experiments

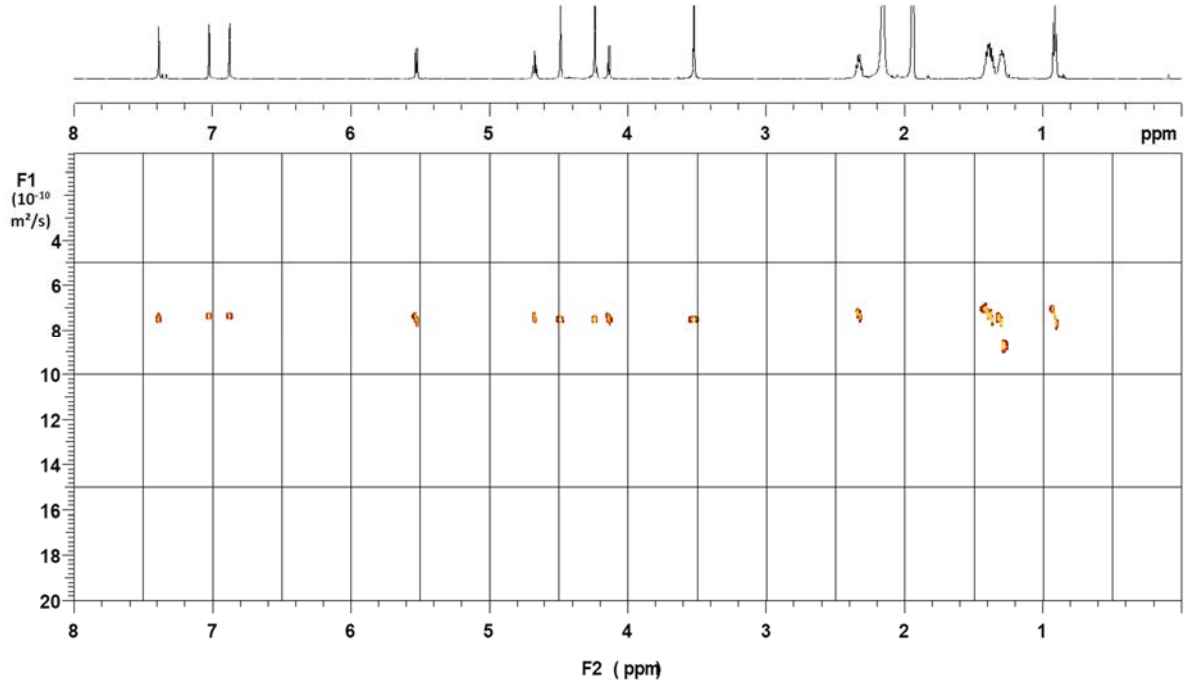

Figure S13. NMR DOSY spectrum of **Rim$_4$** (600 MHz, CD_3CN, 300 K).

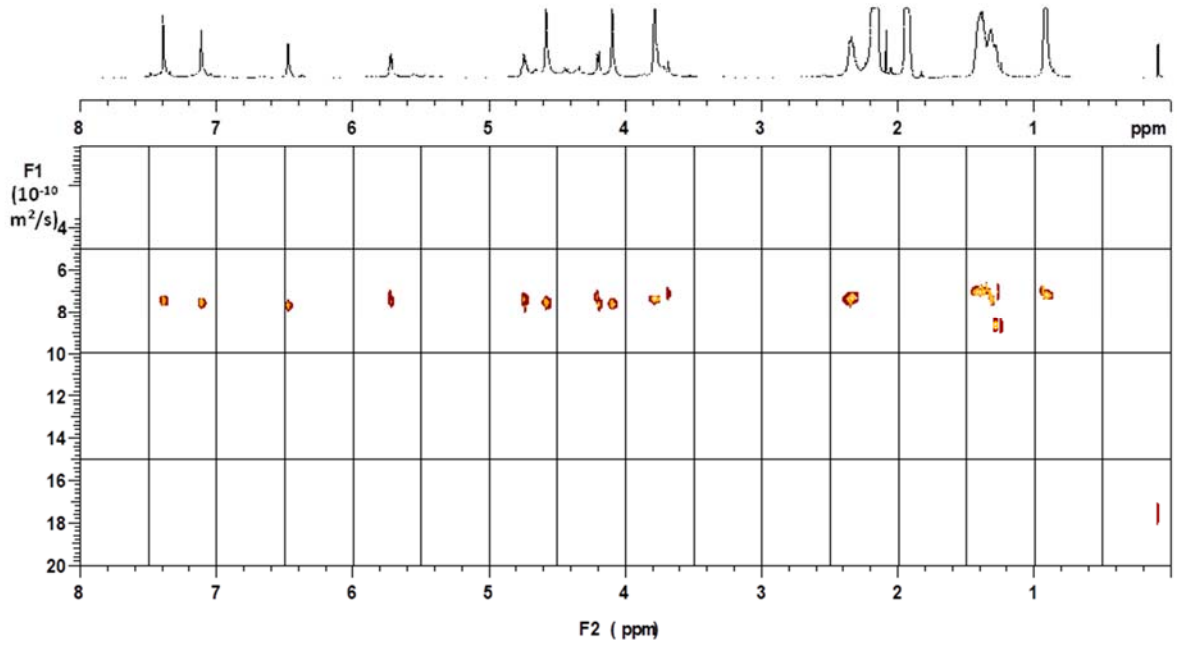

Figure S14. NMR DOSY spectrum of [**Rim**$_4$ZnS]$(ClO_4)_2$ (600 MHz, CD_3CN, 300 K).

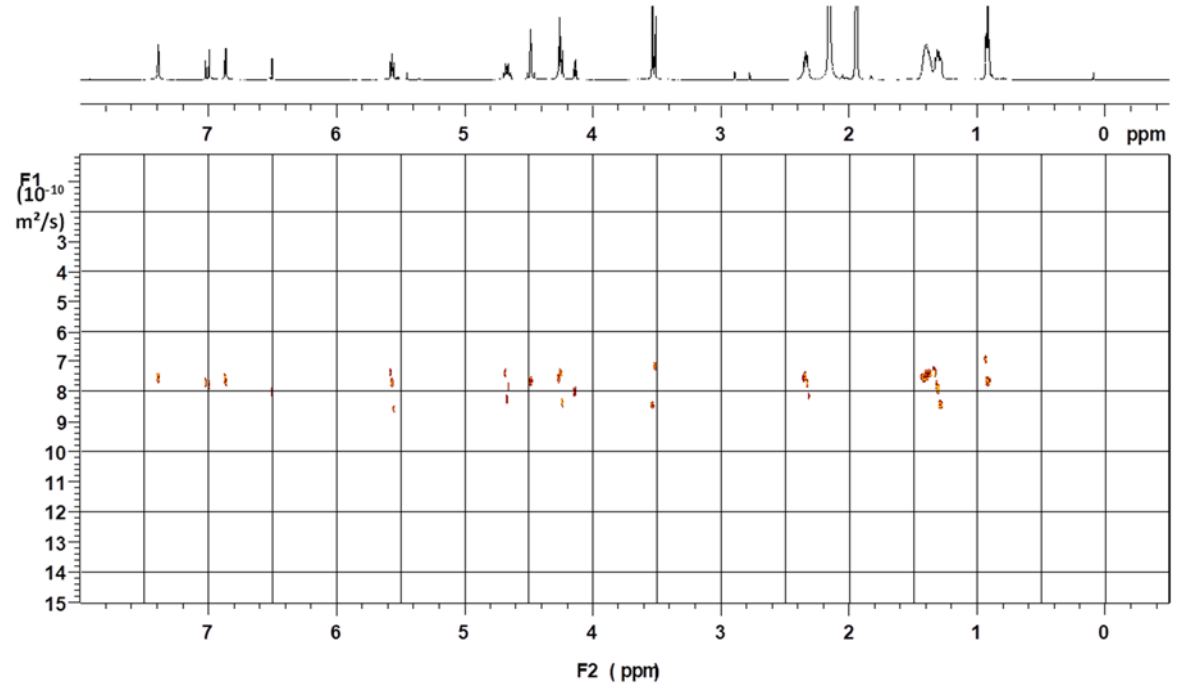

Figure S15. NMR DOSY experiment on **Rim$_3$** (600 MHz, CD_3CN, 300 K).

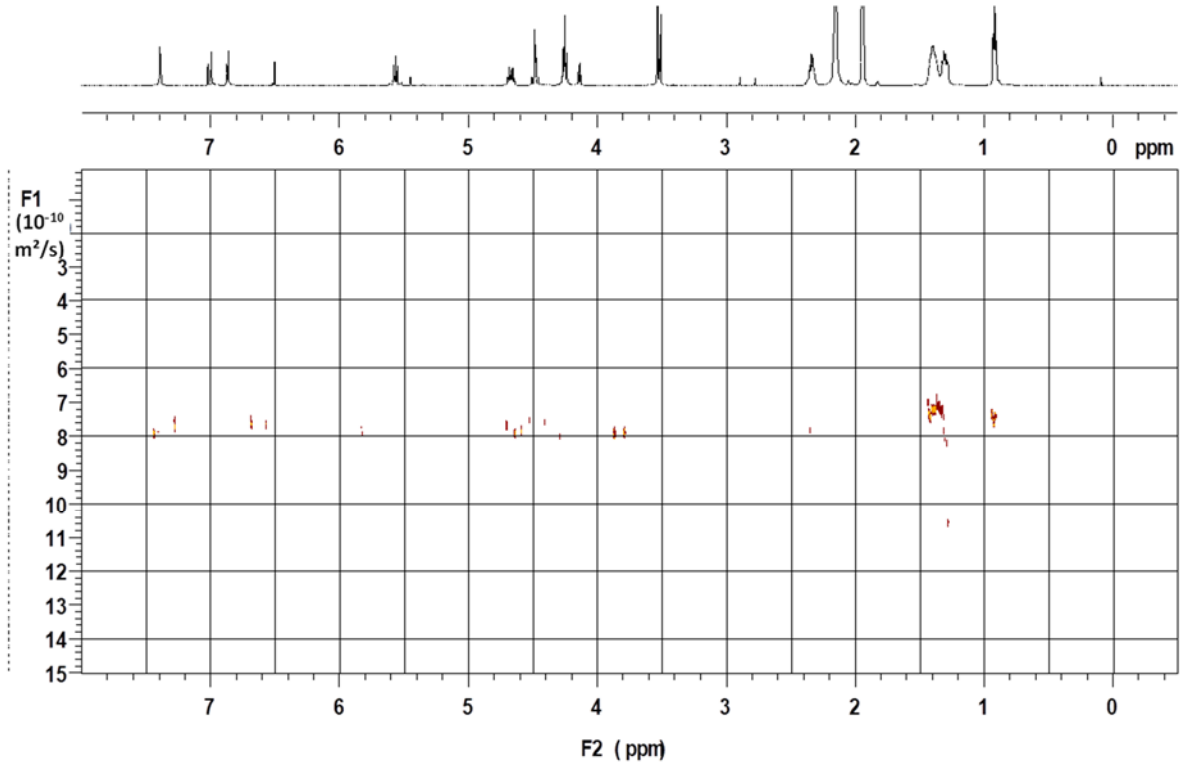

Figure S16. NMR DOSY spectrum of [**Rim**$_3$ZnS](ClO$_4$)$_2$ (600 MHz, CD$_3$CN, 300 K).

3. ITC Experiments

Standard procedure: Standard solution (1 mL, 0.05 mM) in dry CH$_3$CN was titrated by an analyte solution (240 µL, 0.5 mM) in dry CH$_3$CN and monitored via ITC. 30 injections of 8 µL with an interval of 300 s were made. Thermodynamic parameters were calculated using an independent model. The first injection was not taken into account.
Note: all precautions that were taken to avoid the presence of water, including at the level of the ITC equipment (drying with argon, filling under argon flux, …).

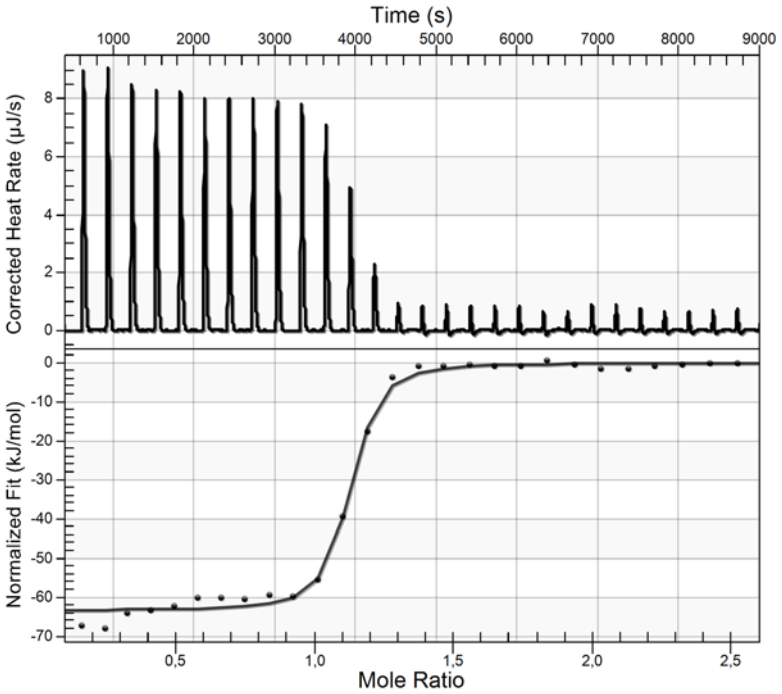

Figure S17. Titration of **Rim$_3$** (0.05 mM) with $Zn(ClO_4)_2.6H_2O$ (0.5 mM). $\Delta H°$ = – 67 ± 5 kJmol^{-1}, $\Delta S°$ = – 102 ± 26 JK^{-1}mol^{-1}, n = 0.9 ± 0.2, K = (6 ± 4) x 10^6 M^{-1}.

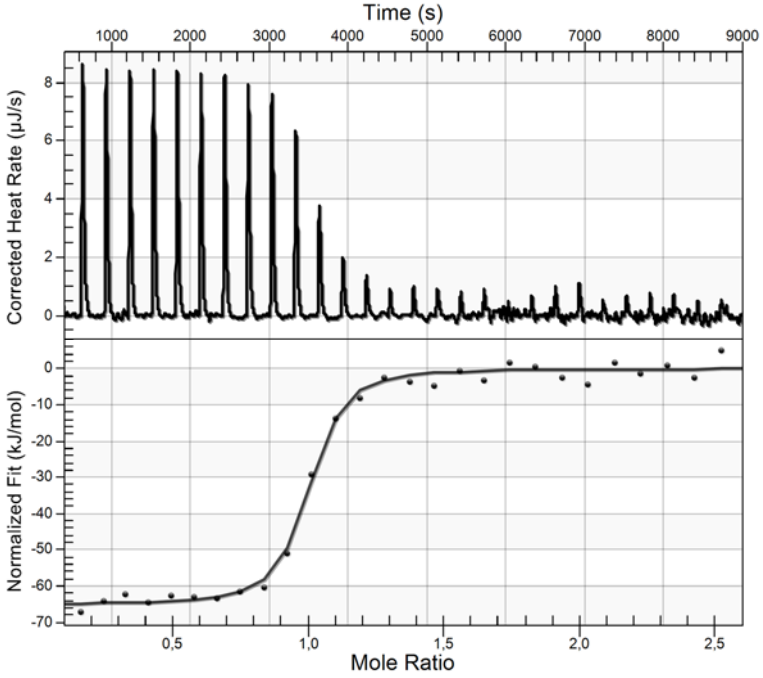

Figure S18. Reverse titration: $Zn(ClO_4)_2.6H_20$ (0.05 mM) with **Rim$_3$** (0.5 mM). $\Delta H°$ = – 67 ± 3 kJmol^{-1}, $\Delta S°$ = – 98 ± 35 JK^{-1}mol^{-1}, n = 1.0 ± 0.1, K = (4 ± 3) x 10^6 M^{-1}.

4. NMR experiments for host-guest and hydration studies

Standard procedure

Titration. [**Rim$_4$**Zn(EtOH)](ClO$_4$)$_2$ (2 mg, 1.3 10^{-3} mmol) was dissolved in CD_3CN (0.4 mL, 3.25 mM) in an NMR tube. Small injections of analytes (10 µL, 1.3 10^{-3} mmol) were made using a 10 µL Hamilton syringe and monitored via NMR.

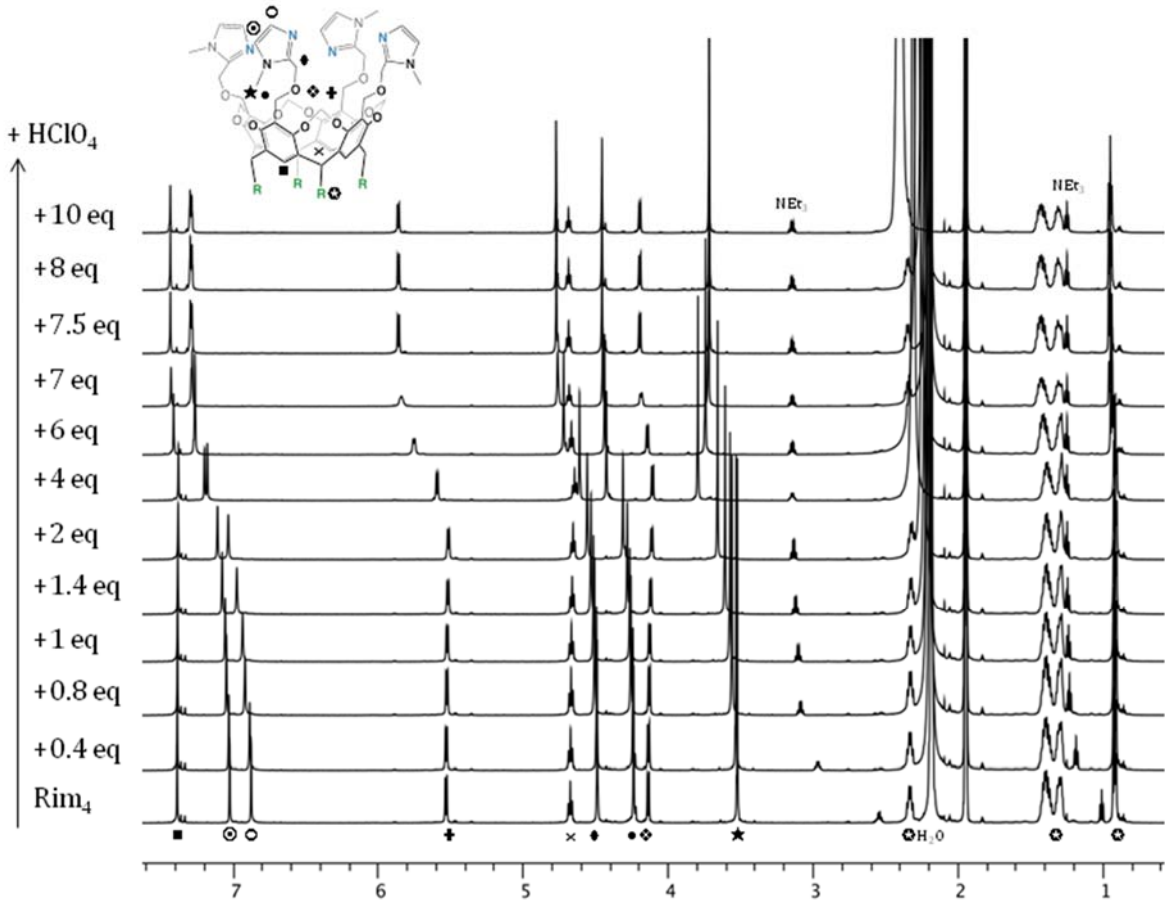

Figure S19. ^{1}H NMR titration (500 MHz, CD_3CN, 300 K) of **Rim$_4$** (2 mM) with perchloric acid.

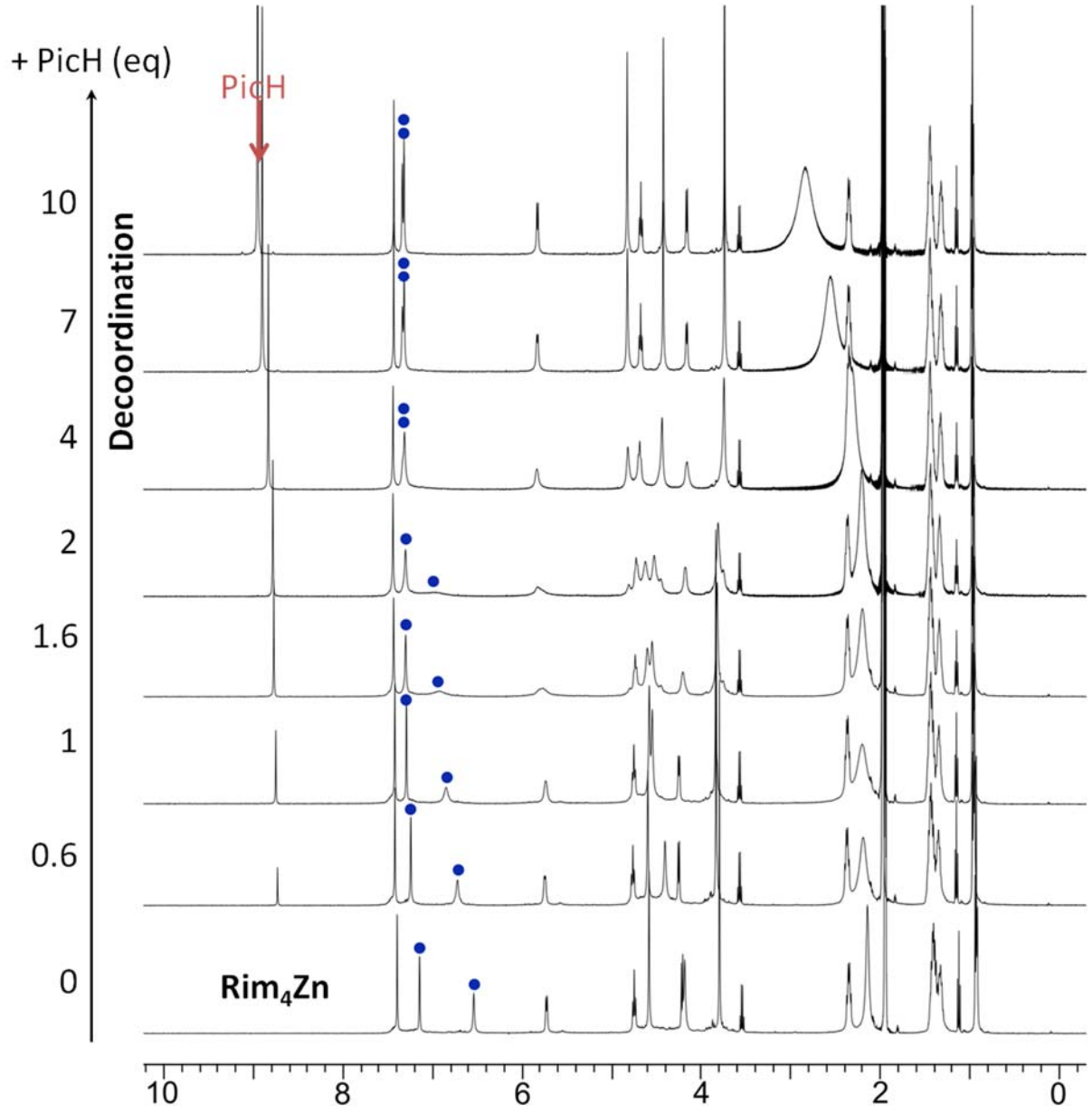

Figure S20 (corresponding to Figure 4). ^{1}H NMR titration (500 MHz, CD_3CN, 300 K) of [**Rim$_4$**Zn(S)]$(ClO_4)_2$ (2 mM) with picric acid. Blue dots: imidazole protons.

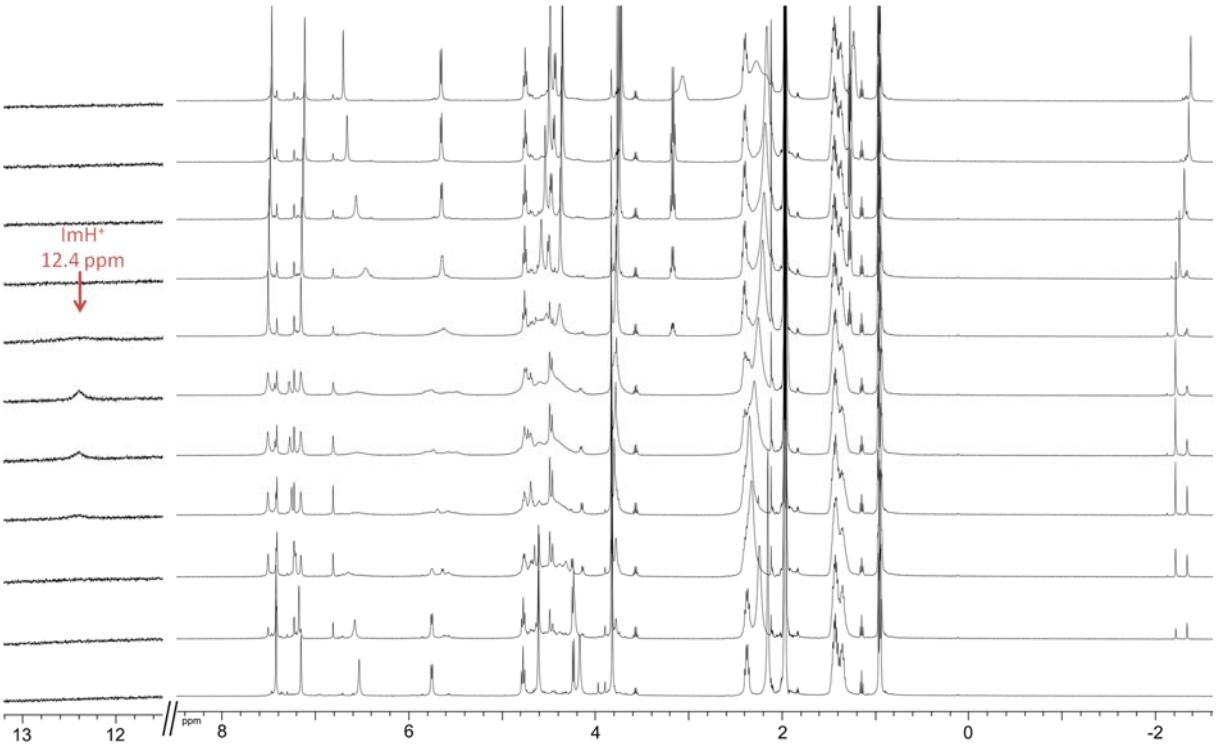

Figure S21 (corresponding to Figure 5). ^{1}H NMR titration (500 MHz, CD_3CN, 300 K) of [**Rim**$_4$Zn(S)]$(ClO_4)_2$ (2 mM) with acetic acid (addition of 0.2 eq of AcOH up to 1 eq, bottom) then NEt_3 (addition of 0.2 eq up to 1 eq, top) (full picture of Figure 5). Left: zoom (x 10) on the 12–13 ppm region.

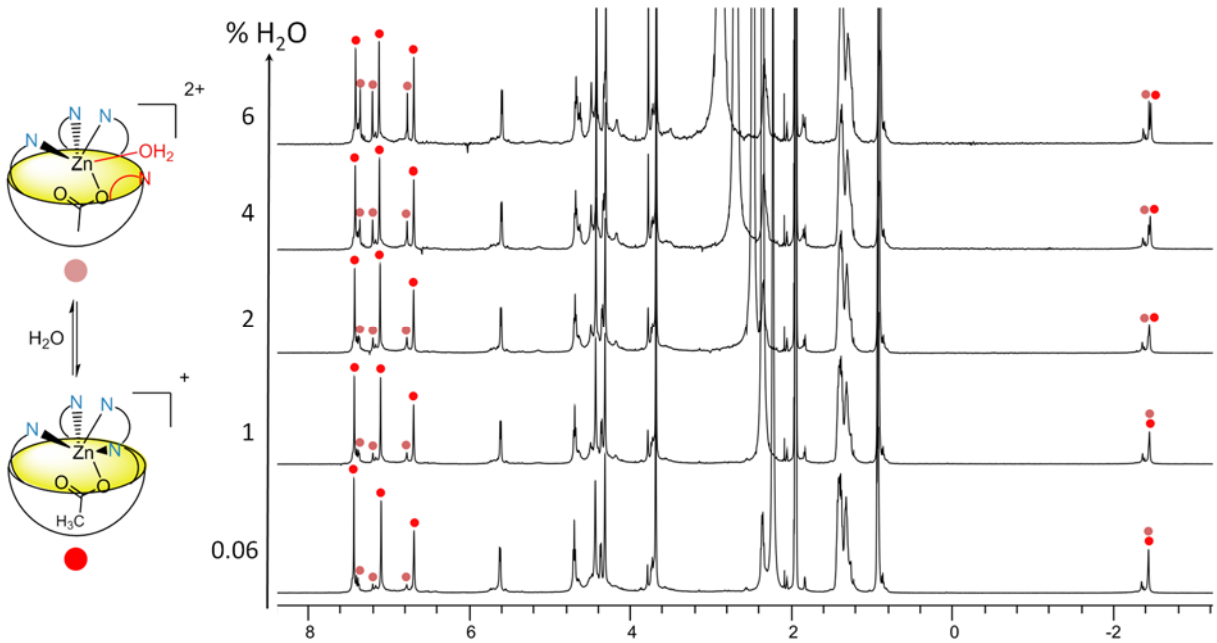

Figure S22. ^{1}H NMR (600 MHz, CD_3CN, 298 K) of [**Rim**$_4$Zn(OAc)]$(ClO_4)_2$ (3 mM) with various water contents (addition of 1 µL up to 30 µL).

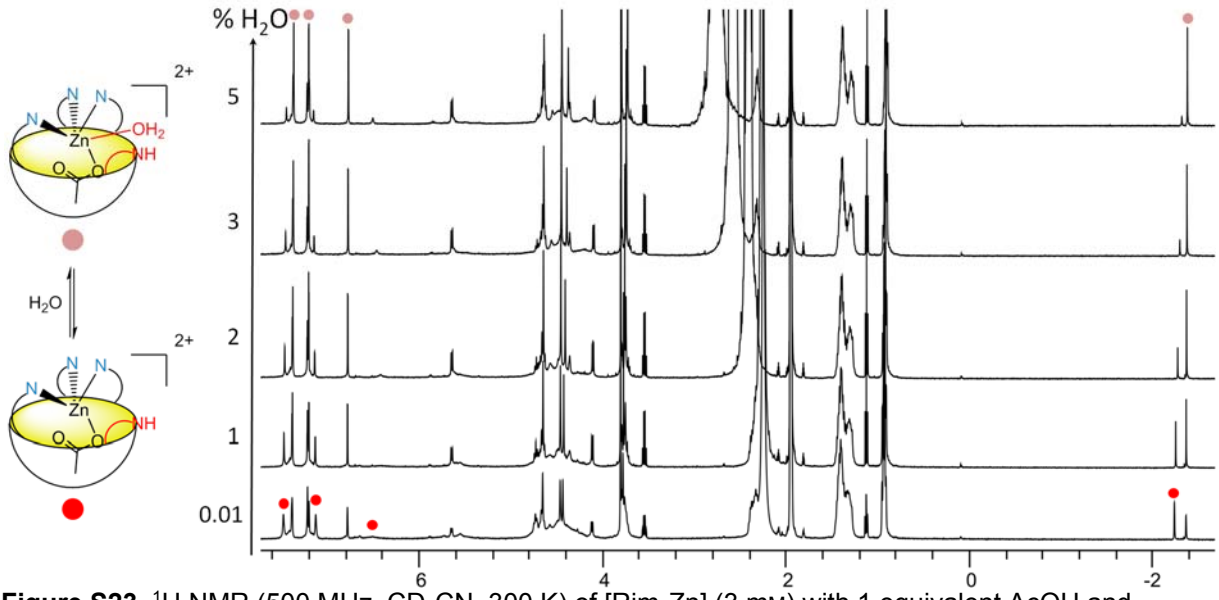

Figure S23. ^{1}H NMR (500 MHz, CD_3CN, 300 K) of [Rim_4Zn] (3 mM) with 1 equivalent AcOH and various water contents (addition of 4 µL up to 28 µL).

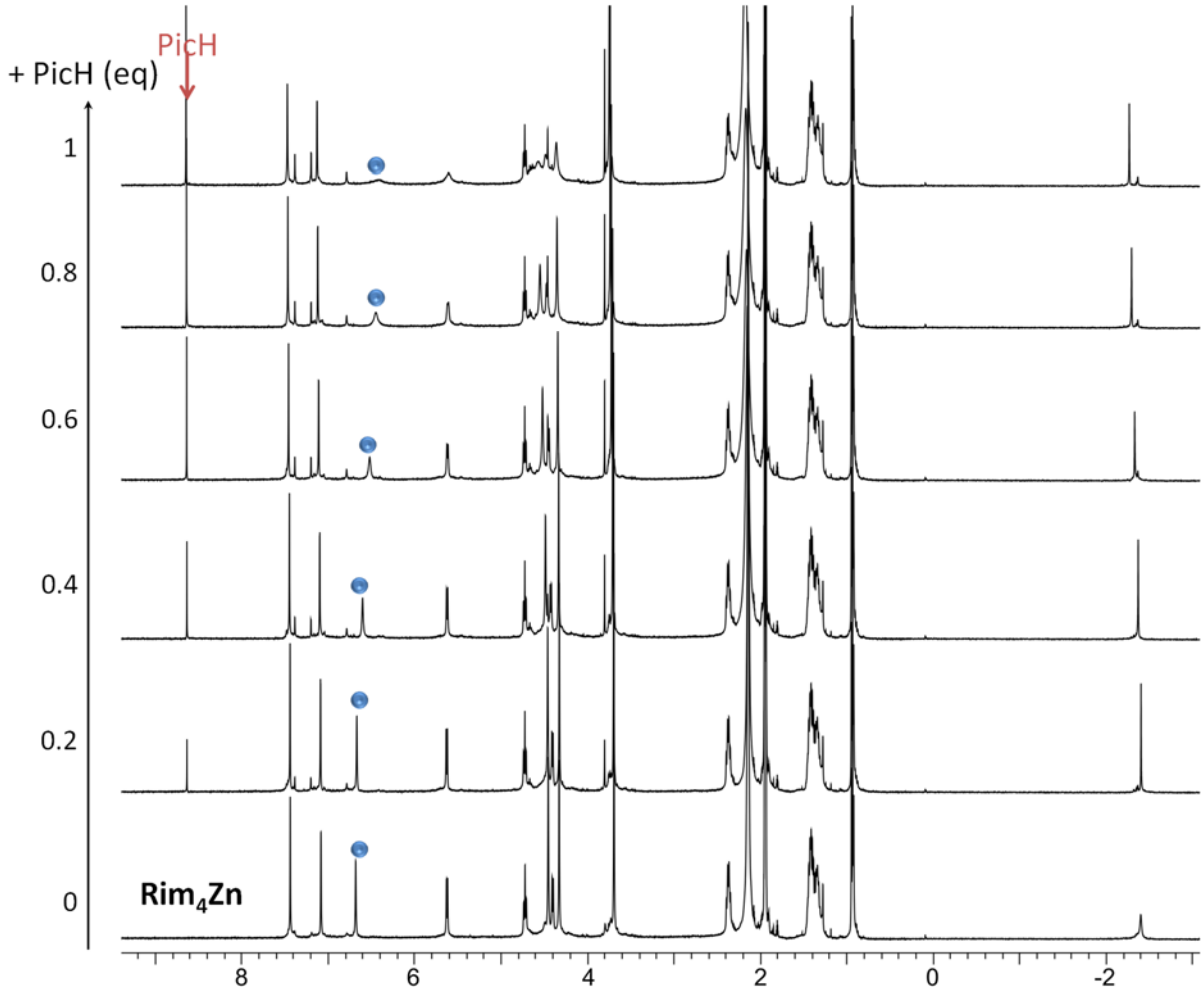

Figure S24. Titration of [**Rim$_4$**Zn(OAc)](ClO_4) (2 mM) with picric acid (^{1}H NMR, 500 MHz, 300 K, CD_3CN). Addition of 0.2 eq of picric acid up to 1 eq. The signal at – 2.40 ppm (included acetate) retains the same integration throughout the titration. Blue dots: one imidazole proton, particularly affected by the acidity of the medium.

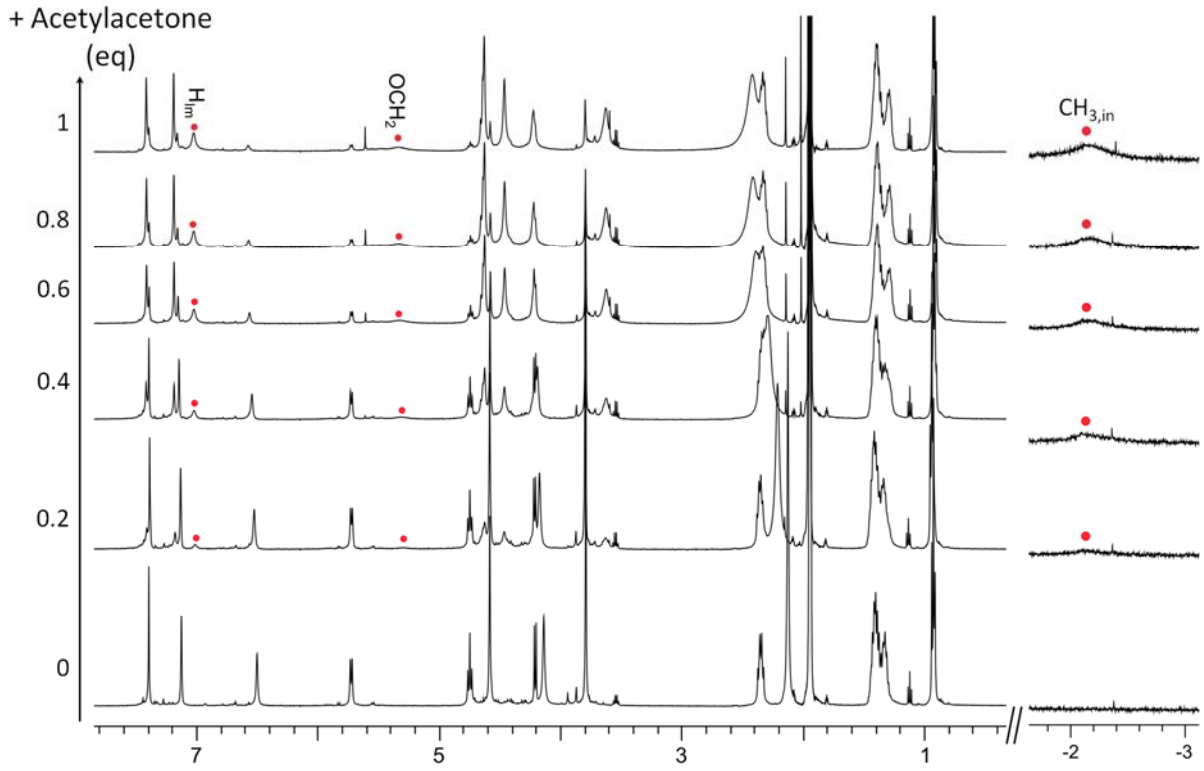

Figure S25. Titration of [**Rim$_4$**Zn(S)](ClO$_4$)$_2$ (2 mM) with acetylacetone. Addition of 0.2 eq of acetylacetone up to 1 eq (red dots: selected resonances for [**Rim$_4$**Zn(acetylacetonate)](ClO$_4$). ^{1}H NMR (250 MHz, CD$_3$CN, 300 K). Right: zoom (x 10) on the – 2 to – 3 ppm region.

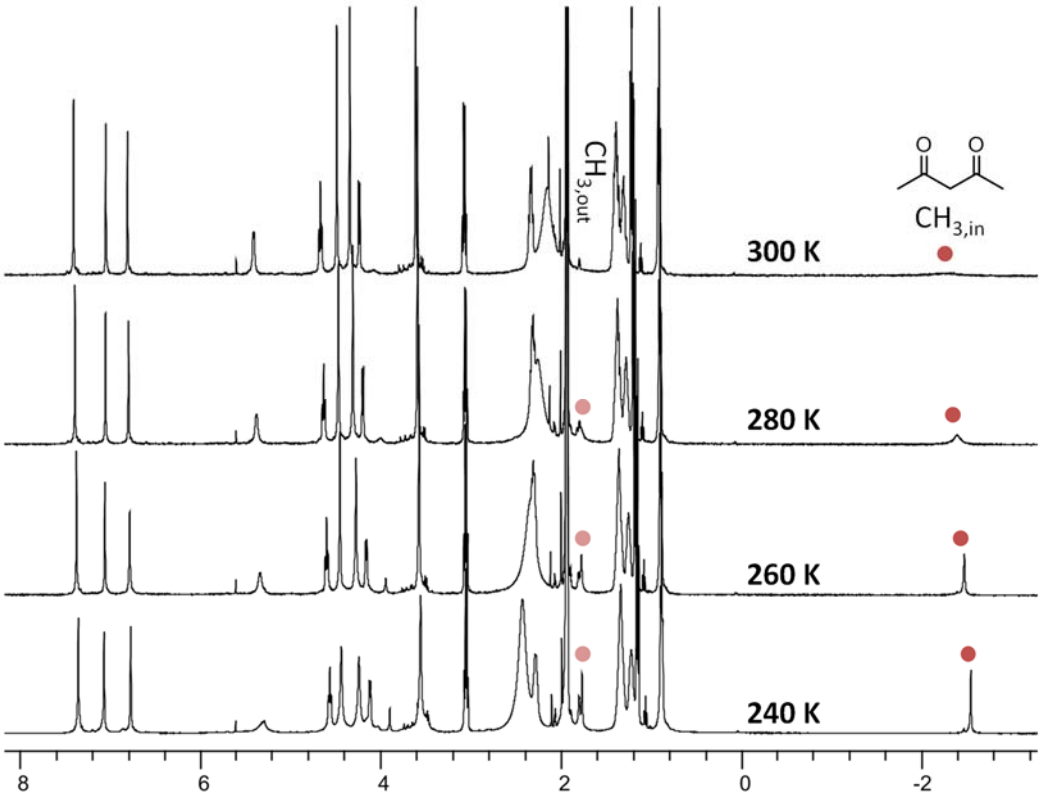

Figure S26. ^{1}H NMR spectra at various *T* of [**Rim$_4$**Zn(acetylacetonate)]$^+$ (2 mM) obtained after addition of 1 eq acetylacetone and 1 eq NEt$_3$ to [**Rim$_4$**Zn(S)](ClO$_4$)$_2$. From bottom to top: 240 K, 260 K, 280 K,

300 K (500 MHz, CD_3CN). The red dots indicate the signal corresponding to the *endo*-bound methyl group of acetylacetonate coordinated to the metal center, and the pink dots indicate the corresponding *exo*-bound methyl group.

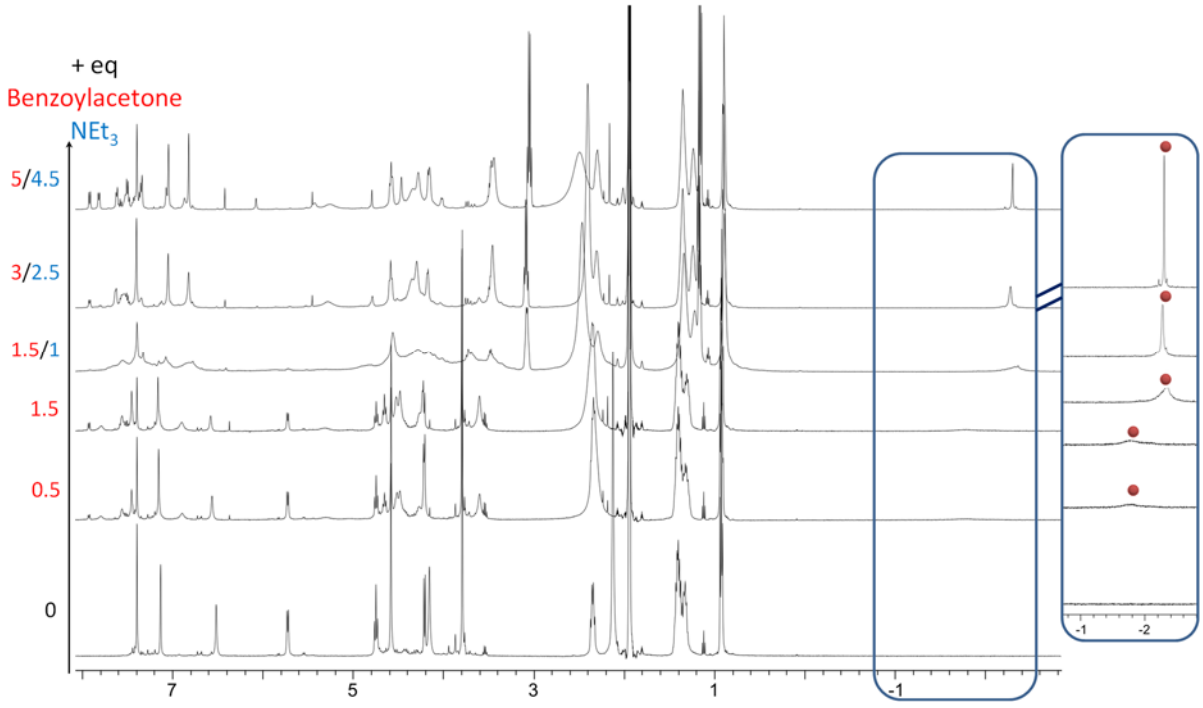

Figure S27. Titration of [**Rim**$_4$Zn(S)]$(ClO_4)_2$ (2 mM) with benzoylacetone then NEt_3. From bottom to top: [**Rim**$_4$Zn(S)]$(ClO_4)_2$, +0.5 eq benzoylacetone, + 1.5 eq, +1.5 eq benzoylacetone/+1 eq NEt_3, +3 eq benzoylacetone/2.5 eq NEt_3, +5 eq benzoylacetone/4.5 eq NEt_3 (500 MHz, CD_3CN, 300 K). Inset: zoomed intracavity region.

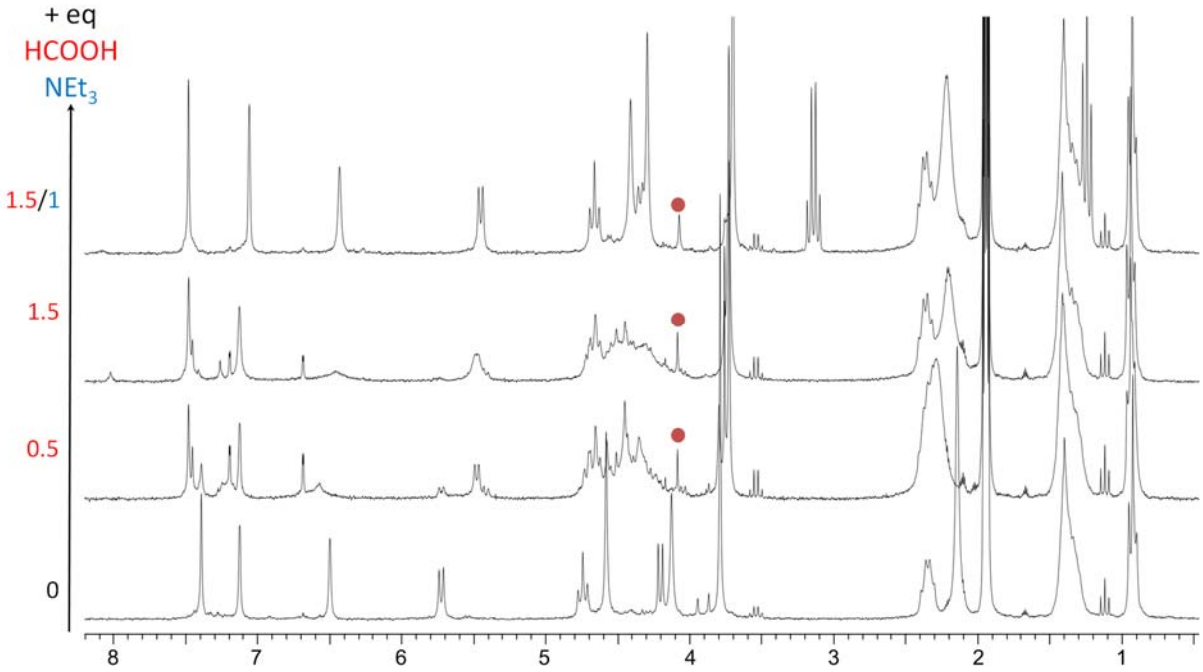

Figure S28. Titration of [**Rim**$_4$Zn(S)]$(ClO_4)_2$ (2 mM) with formic acid then NEt_3. Bottom to top: [**Rim**$_4$Zn(S)]$(ClO_4)_2$, +0.5 eq formic acid, +1.5 eq formic acid, +1.5 eq formic acid/+1 eq NEt_3 (250 MHz, CD_3CN, 300 K). Red dots indicate the signal for included formate.

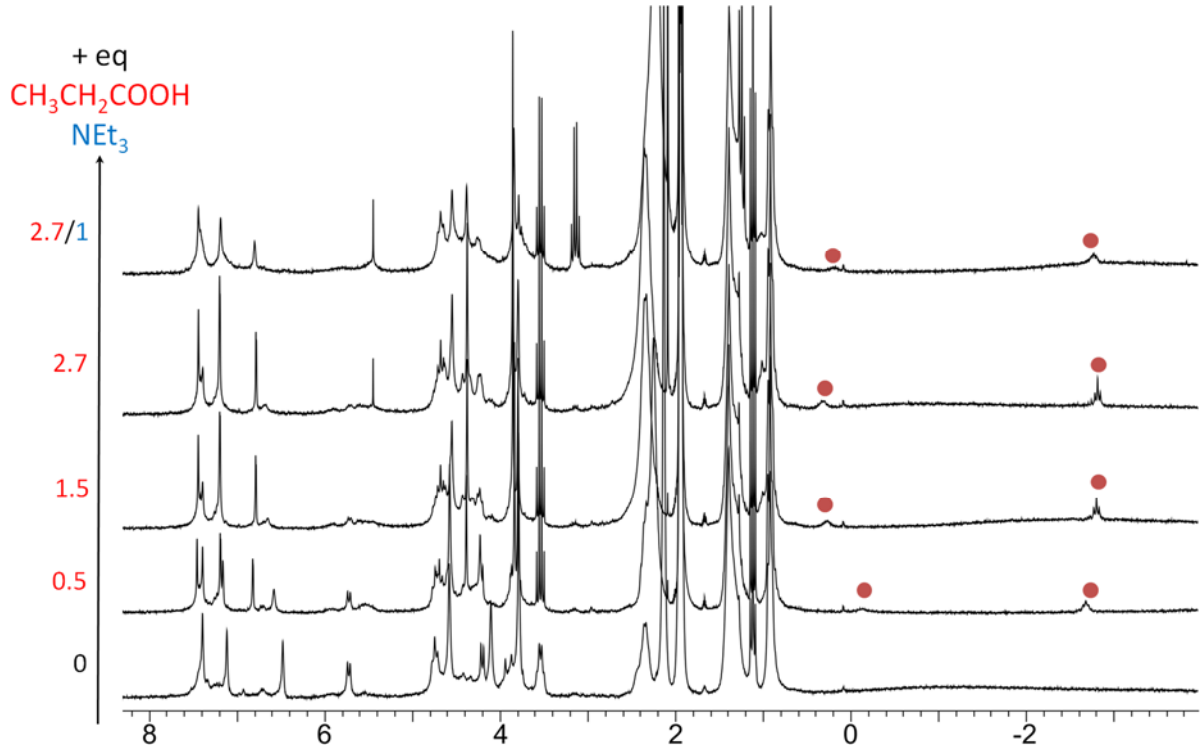

Figure S29. Titration of [**Rim**$_4$Zn(S)](ClO$_4$)$_2$ (2 mM) with propionic acid then NEt$_3$. From bottom to top: [**Rim**$_4$Zn(S)](ClO$_4$)$_2$, +0.5 eq propionic acid, +1.5 eq propionic acid, +2.7 eq propionic acid, +2.7 eq propionic acid/+1 eq NEt$_3$ (250 MHz, CD$_3$CN, 300 K). Red dots indicate included propionate.

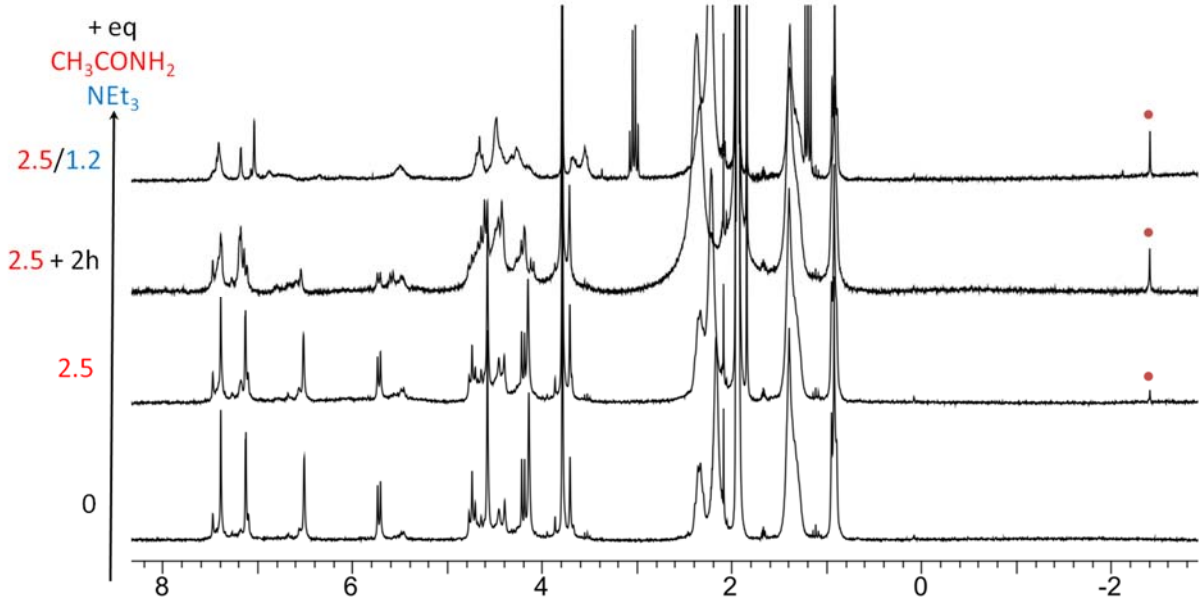

Figure S30. Titration of [**Rim**$_4$Zn(S)](ClO$_4$)$_2$ (2 mM) with acetamide then NEt$_3$. From bottom to top: [**Rim**$_4$Zn(S)](ClO$_4$)$_2$, +2.5 eq acetamide, after 2 h at RT, +1.2 eq NEt$_3$. ^{1}H NMR (250 MHz, CD$_3$CN, 300 K). Red dots indicate included acetamide.

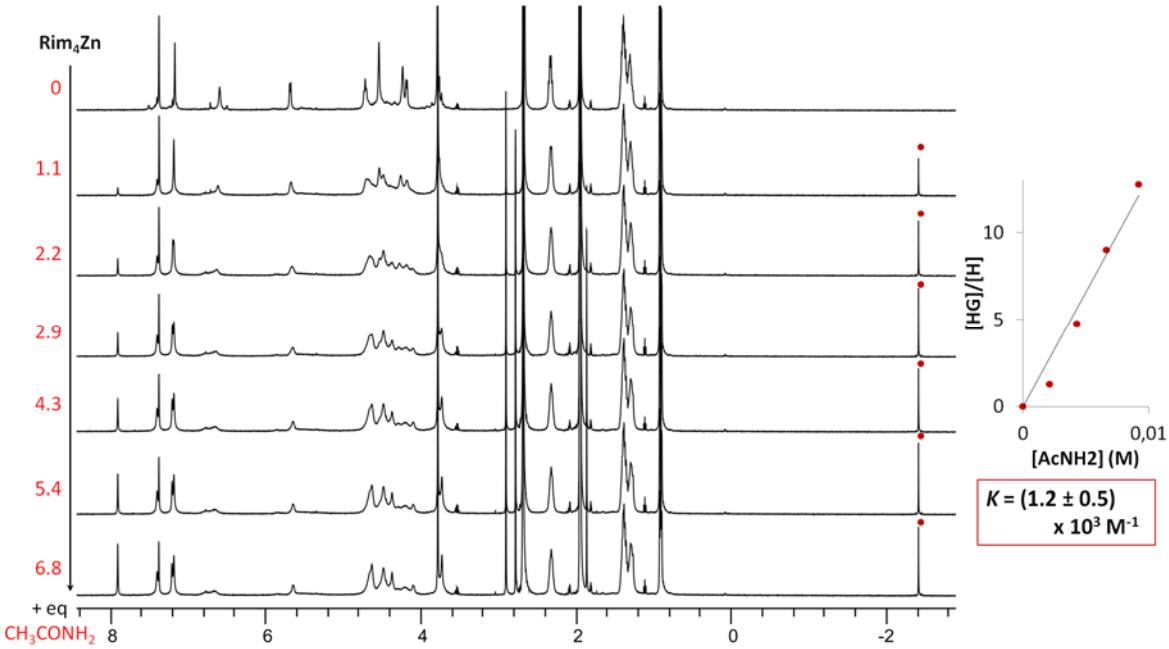

Figure S31. Titration of [**Rim**$_4$Zn(S)](ClO$_4$)$_2$ (1 mM) with acetamide (with DMF as reference for quantification) and determination of the associated binding constant (the concentrations were determined by integration of the peaks corresponding to included acetamide, free acetamide and DMF). ^{1}H NMR (500 MHz, CD$_3$CN/D$_2$O 95:5, 300 K)**.** Red dots indicate included acetamide.

Kinetic measurements. [**Rim**$_4$Zn(EtOH)](ClO$_4$)$_2$ (2.1 mg, 3 mM) was dissolved in 0.5 mL of CH$_3$CN/CD$_3$CN (8:2) and water (5 to 35%) in an NMR tube with DMF (5.2 mM) as a reference for integrations. The tube was rapidly introduced in a 500 MHz NMR spectrometer set at 343 K and spectra (6 scans) were recorded every 30 s. The growing intracavity signal at -2.40 ppm was integrated to follow and quantify acetamide formation.
The tube was then heated for 8 days at 343 K and NMR spectra (32 scans) were recorded twice a day. The integration of the amide NH protons allowed to quantify acetamide formation over time.
A previously reported equation for catalysis inhibited by product displacement[3] was used to fit the kinetic data and extract reaction rates:

$$[AcNH_2](t) = v_2 t - \frac{(v_2 - v_1)(1 - e^{-kt})}{k}$$

with v_1 and v_2 the reaction rates characteristic for the first and second phase, respectively, and k the rate constant characteristic for the burst (first) phase.

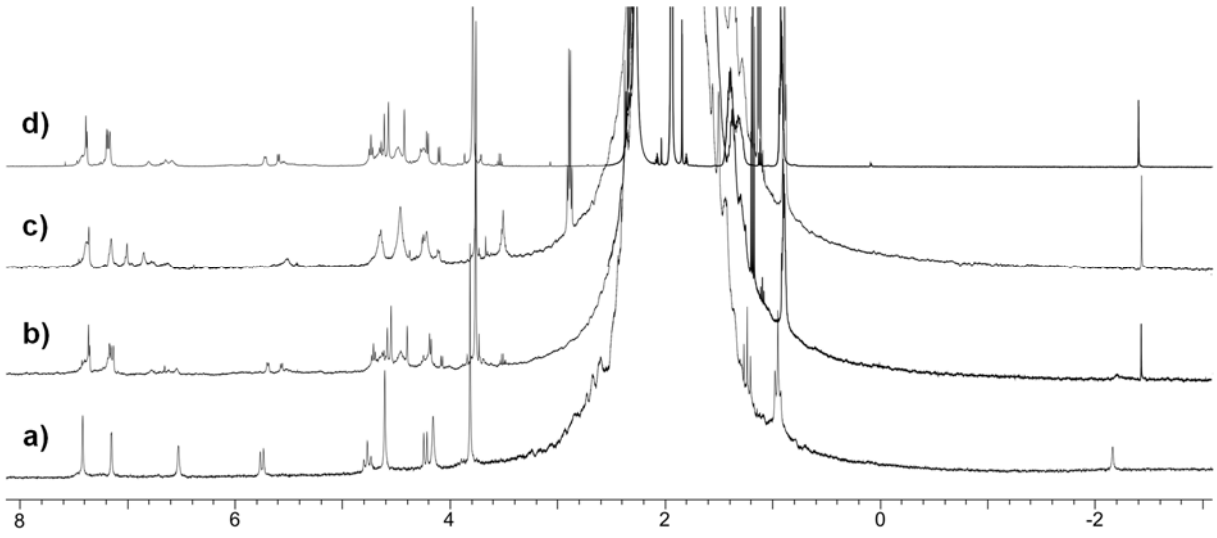

Figure S32 (corresponding to the full spectra of Figure 6). a) [**Rim$_4$**Zn(S)](ClO$_4$)$_2$ (2 mM), b) after 14 days at 70 °C, c) [**Rim$_4$**Zn(S)](ClO$_4$)$_2$ after 14 days at 70 °C +1.5 eq NEt$_3$, d) [**Rim$_4$**Zn(S)](ClO$_4$)$_2$ + 1.5 eq acetamide. ^{1}H NMR (500 MHz, CH$_3$CN/CD$_3$CN 95:5, 300 K).

Evidences for the accumulation of acetamide in the acetonitrile solution of the [Rim$_4$Zn(S)](ClO$_4$)$_2$ complex after heating at 70°C.

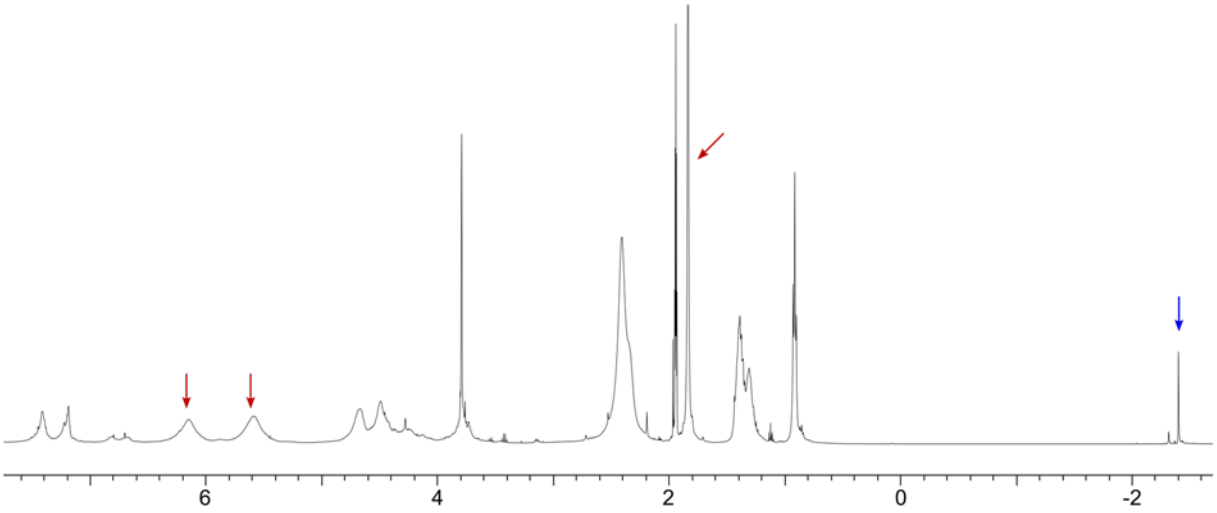

Figure S33. ^{1}H NMR spectrum of [**Rim$_4$**Zn(S)](ClO$_4$)$_2$ after 6 days at 70 °C. [**Rim$_4$**Zn(AcNH)]$^+$ has formed (blue arrow), and signals corresponding to free acetamide have appeared (red arrows). ^{1}H NMR (500 MHz, CD$_3$CN, 300 K).

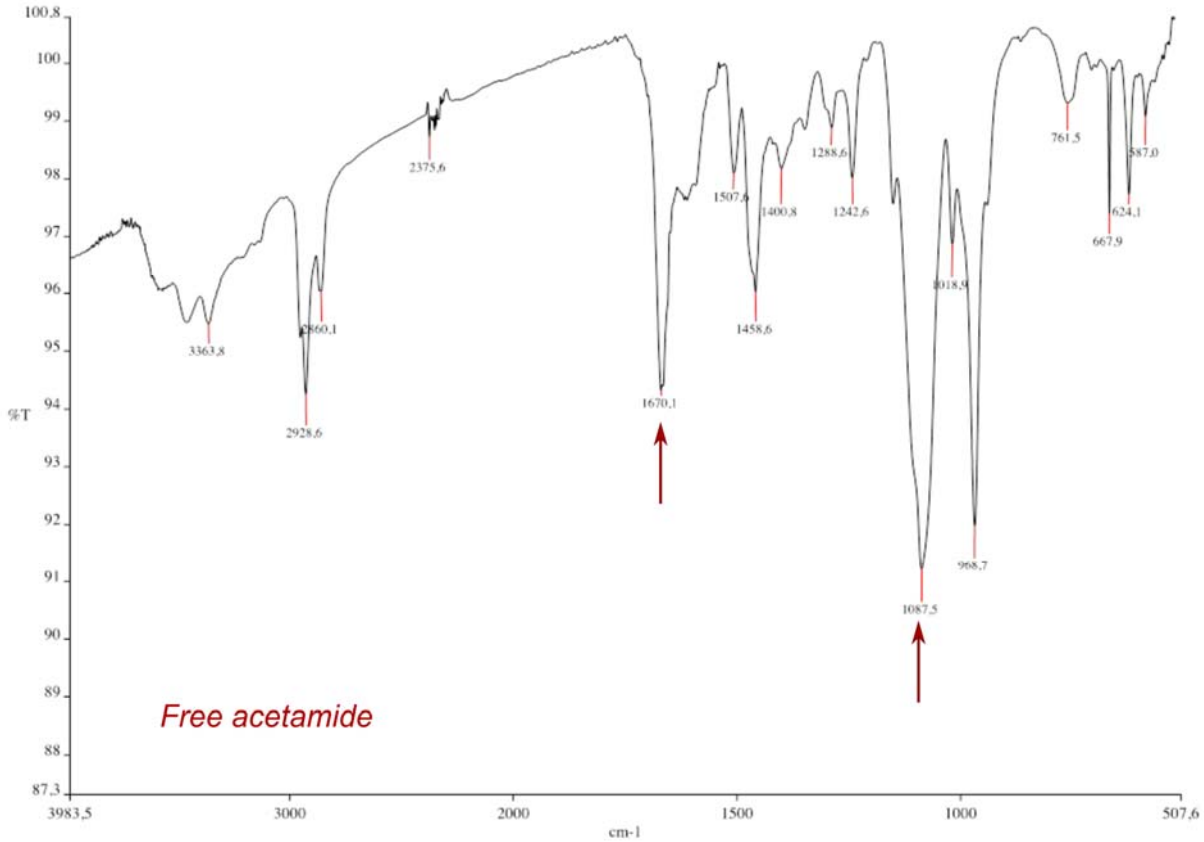

Figure S34. IR spectrum of [**Rim$_4$**Zn(S)](ClO$_4$)$_2$ heated for 14 days at 70 °C, KBr pellet. The red arrows indicate the presence of free acetamide.

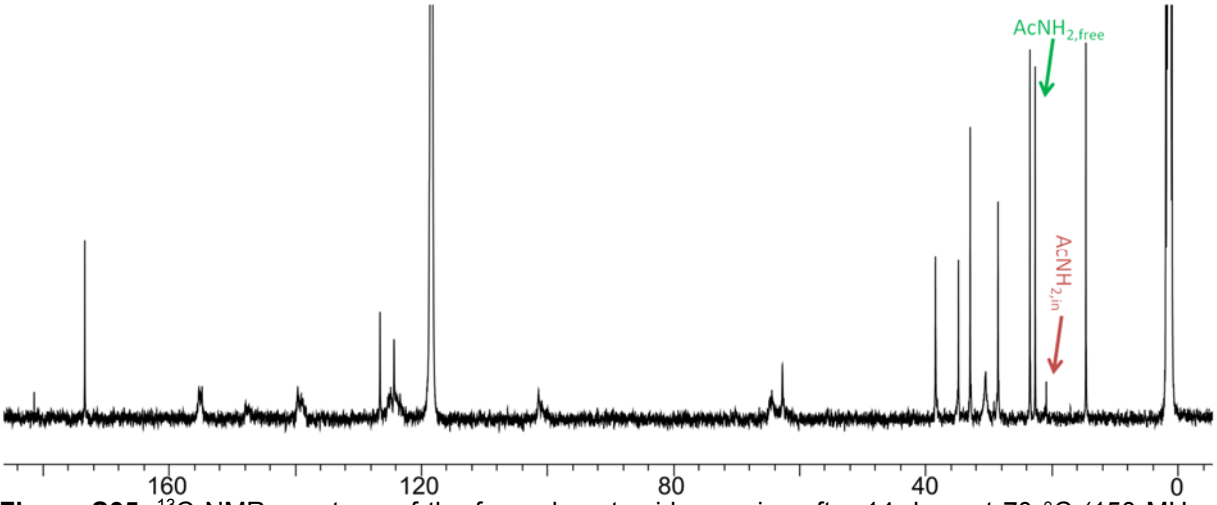

Figure S35. ^{13}C NMR spectrum of the formed acetamido species after 14 days at 70 °C (150 MHz, CD_3CN, 300 K).

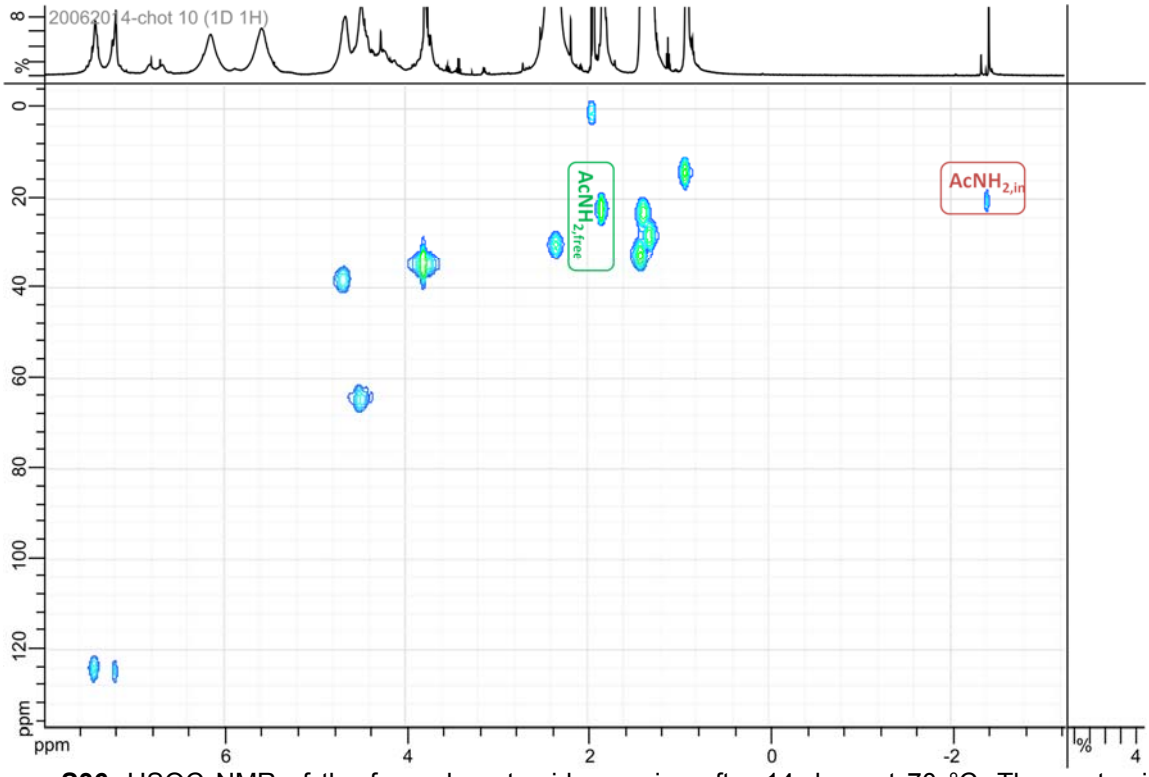

Figure S36. HSQC NMR of the formed acetamido species after 14 days at 70 °C. The acetamido complex formation is confirmed by the presence of a high-field signal characteristic of included acetamide (highlighted in pink) and of a singlet of free acetamide (highlighted in green).

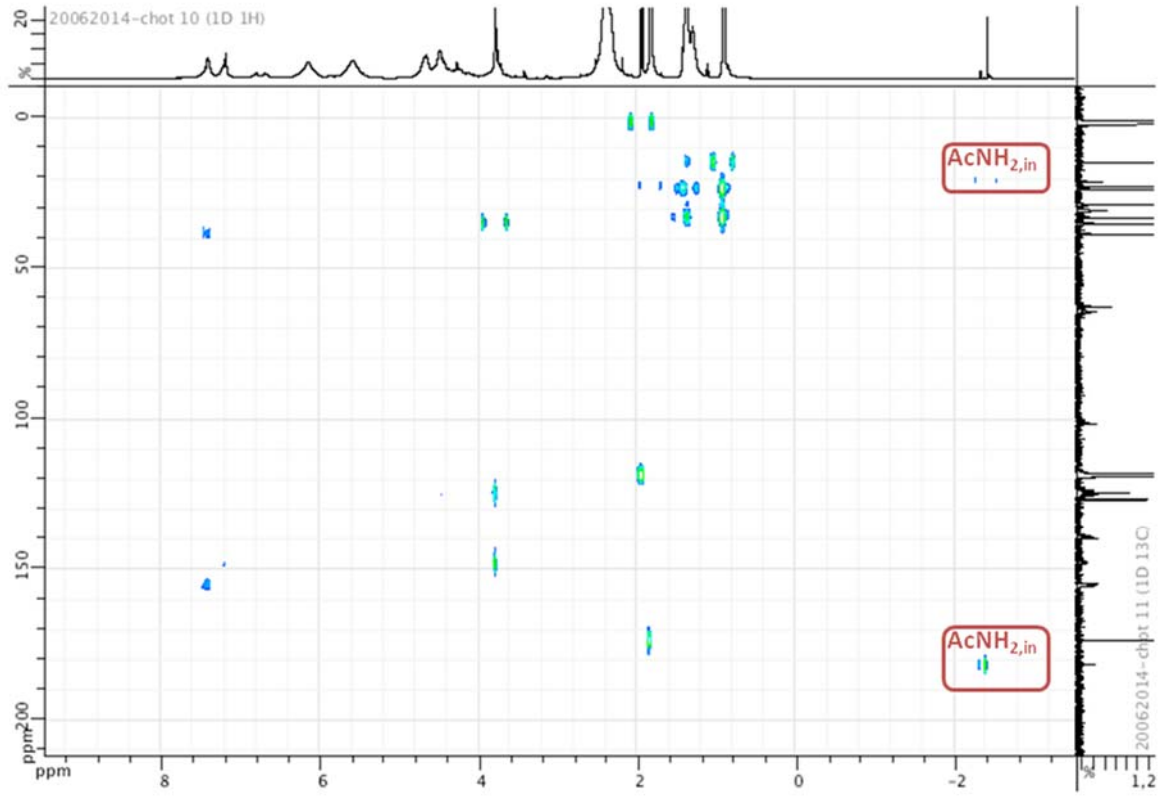

Figure S37. HMBC NMR spectrum of the formed acetamido species after 14 days at 70 °C. The acetamido complex formation is confirmed by the presence of a high-field signal characteristic of included acetamide (highlighted in pink).

---

[1] C. B. Reese, Z. Pei-Zhuo, *J. Chem. Soc. Perkin Trans 1* **1993**, 2291-2301.
[2] H. El Moll, D. Semeril, D. Matt, M.-T. Youinoub, L. Toupet, *Org. Biomol. Chem.*, **2009**, *7*, 495-501.
[3] C. Frieden. *J. Biol. Chem.*, **1970**, *245*, 5788-5799.